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BLOOD ELECTROLYTES IN PROLONGED LABOUR

BY

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THE present work was undertaken to ascertain some of the changes that occur in the *milieu intérieur* during prolonged labour. Twenty-nine patients in whom the first stage of labour lasted more than 24 hours were studied. They were subject to the usual obstetric management, Caesarean section being performed for such indications as foetal or maternal distress, or failure of progressive cervical dilatation. One or two patients who by clinical criteria became dehydrated were given parenteral fluids and withdrawn from the study.

The observations, therefore, represent changes occurring during prolonged labour, at a time when progress appeared to be, from a purely clinical point of view, satisfactory in all respects other than the duration of the labour. An attempt will be made to assess which of these changes can be regarded as physiological adaptation, and which can be regarded as undesirable consequences of, or contributory factors to, the prolongation of labour.

In order to indicate trends, the results are presented as mean curves and related to observations made on patients at term (39 to 40 weeks) but not in labour. Blood samples were taken in labour at intervals of about 12 hours as far as possible, but isolated observations only could be made on some of the patients.

A few results obtained from patients in labour for less than 24 hours and some from patients one to two weeks post-partum are also considered. To assist in interpretation of the results some observations on the circulating eosinophil count during labour are presented.

METHODS

The majority of the observations on plasma electrolytes were made on heparin plasma. Ten ml. specimens of blood were added to bottles containing approximately 0·2 mg. of solid heparin, and the plasma separated within one hour. In a few cases serum was used for estimations other than those of potassium. Specimens of plasma or serum showing haemolysis were rejected.

Plasma water was measured by weight loss on drying 0·5 ml. samples in small thin-walled tubes at 105° C. for 16 hours, weighing to the nearest 0·1 mg. Plasma specific gravity was measured by the copper sulphate method (Phillips *et al.*, 1950). Plasma chloride was estimated by the method of Keys (1937) using 0·5 ml. of plasma and acid digestion for 1 hour; flame photometry was used for sodium and potassium. Plasma calcium was determined by the method of Kramer and Tisdall (1921), magnesium being estimated on the supernatants from the calcium determinations, as described by Simonsen, Westover and Wertman (1947).

Packed red cells were obtained after centrifuging the heparinized blood, and estimations performed on 0·2 ml. aliquots. The method of Keys (1937), with a 60-minute acid digestion, was used for red cell chlorides. Red cell sodium and potassium were estimated by flame photometry on aliquots which had been digested for 60 minutes in 2 ml. of 50 per cent nitric acid, with the addition of 1 drop of 100 vol. hydrogen peroxide each 30 minutes.

TABLE I
Cases of Prolonged Labour, Classified According to Outcome

Duration of First Stage (hours)	No. of Cases	Spontaneous Delivery	Forceps Delivery for	
			Foetal Distress	Delay
(a) *Vaginal Deliveries (13)*				
24–39 ..	5	3	1	1
40–59 ..	5	4	–	1
60–90 ..	3	–	1	2

Duration of First Stage (hours)	No. of Cases	Indication for Caesarean Section	
		Foetal Distress	Delay
(b) *Caesarean section (16)*			
24–39	4	1	3
40–59	7	1	6
60–89	3	–	3
90–120	2	–	2

The onset of labour was taken from the time of onset of regular and progressive uterine contractions. When this was uncertain it was taken from the time at which progressive dilatation of the cervix started.

The cases of prolonged labour are summarized in Table I. Our interest was mainly in cases of prolonged labour which ended in Caesarean section; this accounts for the apparently high incidence of operative deliveries appearing in this table.

All the patients were between 23 and 34 years of age. Of the 13 who eventually had vaginal deliveries, 3 were multiparous; of the 16 who were delivered abdominally none had had previous vaginal deliveries though 2 had previously had Caesarean section.

The patients were all at term but for 2 who had gone into labour spontaneously at 37 weeks. Labour was induced (by sweeping the membranes) in 2 of the patients who had vaginal deliveries, and in 6 of the patients who had Caesarean sections (membranes swept—2; pitocin drip—2; low rupture of membranes —2).

There were no stillbirths or neonatal deaths. All the babies were mature, 24 out of the 29 weighing 7½ pounds (3,400 g.) or more. Of the 12 patients who had labours lasting longer than 40 hours, terminating in Caesarean section for delay, 8 produced babies weighing 9 pounds (4,080 g.) or more, the largest being 10¼ pounds (4,650 g.).

The plasma electrolyte values shown in Figs. 1 to 5 represent some 60 full analyses. Each point on each curve represents the mean of at least five observations; standard errors are indicated. Accurate statistical evaluation of this type of data is not simple and the statistical procedure used must be regarded as approximate. In fact, "t" tests were applied to each point on the mean curves in Figs. 1 to 5, testing for a significant difference from the value determined on patients 40-weeks pregnant but not in labour. For each trend mentioned in the next section, representative points on the mean curve differ significantly ($P=0{\cdot}05$) from the corresponding value in Table II.

RESULTS

The mean values for electrolytes determined on blood samples from a number of patients at term (39–40 weeks), but not in labour, are shown with standard deviations in Table II. The reference levels shown in Figs. 1 to 5 are the mean values from Table II together with their standard errors, and it is the changes from

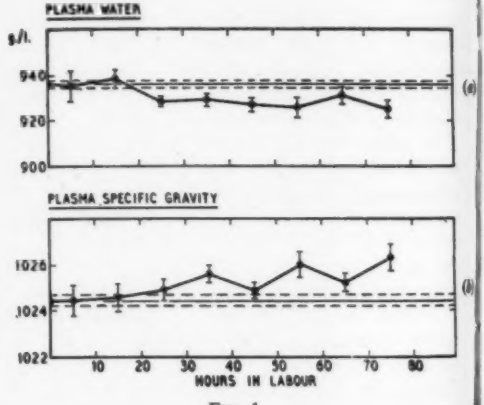

FIG. 1
Plasma water and specific gravity in prolonged labour.

TABLE II

Blood Electrolytes in Patients at Term (39–40 Weeks) But Not in Labour

	Mean	Standard Deviation (No. of Cases)
Plasma water (g./l.)	935·6	±8·2 (26)
Plasma S.G.	1,024·4	±1·5 (29)
Packed cell volume (per cent)	41·0	±3·5 (7)
Plasma chloride (meq./l.)	107·7	±3·7 (22)
Plasma (meq./kg. plasma H_2O)	115·5	±4·2 (22)
Plasma sodium (meq./l.)	134·4	±4·6 (25)
Plasma (meq./kg. plasma H_2O)	143·7	±5·2 (25)
Plasma potassium (meq./l.)	4·19	±0·34 (21)
Plasma (meq./kg. plasma H_2O)	4·48	±0·37 (21)
Plasma calcium (meq./l.)	5·21	±0·85 (23)
Ca^{++} ion (meq./kg. plasma H_2O)	2·55	±0·49 (23)
Plasma magnesium (meq./l.)	1·86	±0·40 (19)
$Mg.^{++}$ ion (meq./kg. plasma H_2O)	1·32	±0·30 (19)
R.B.C. chloride (meq./l. cells)	73·9	±5·7 (11)
R.B.C. sodium (meq./l. cells)	36·7	±11·6 (18)
R.B.C. potassium (meq./l. cells)	96·9	±17·0 (18)
Plasma K^+/Na^+ ratio	0·0312	±0·0027 (20)
R.B.C. K^+/Na^+ ratio	2·89	±1·05 (17)

TABLE III

Blood Electrolytes in the Puerperium

	Mean	Standard Deviation (No. of Cases)	Difference from Values in Late Pregnancy
Plasma water (g./l.)	935·0	±7·1 (7)	—
Plasma S.G.	1,026·0	±1·5 (7)	Significant rise ($P<0·05$)
Packed cell volume (per cent)	37·5	±3·6 (6)	—
Plasma chloride (meq./l.)	105·7	±3·4 (7)	—
Plasma (meq./kg. plasma H_2O)	113·1	±3·2 (7)	—
Plasma sodium (meq./l.)	140·7	±4·1 (7)	Significant rise ($P<0·01$)
Plasma (meq./kg. plasma H_2O)	150·6	±4·8 (7)	Significant rise ($P<0·01$)
Plasma potassium (meq./l.)	4·35	±0·27 (6)	—
Plasma (meq./kg. plasma H_2O)	4·69	±0·24 (6)	—
Plasma calcium (meq./l.)	4·86	±0·57 (5)	—
Ca^{++} ion (meq./kg. plasma H_2O)	2·26	±0·21 (5)	Significant fall ($P<0·05$)
Plasma magnesium (meq./l.)	1·95	±0·33 (6)	—
$Mg.^{++}$ ion (meq./kg. plasma H_2O)	1·33	±0·22 (6)	—
R.B.C. chloride (meq./l. cells)	72·1	±11·4 (7)	—
R.B.C. sodium (meq./l. cells)	33·6	±10·3 (7)	—
R.B.C. potassium (meq./l. cells)	107·2	±5·0 (6)	Significant rise ($P<0·05$)
Plasma K^+/Na^+ ratio	0·0312	±0·0020 (6)	—
R.B.C. K^+/Na^+ ratio	3·73	±1·30 (7)	—

these levels that occur in prolonged labour which will be considered.

Plasma Water and Plasma Specific Gravity

Fig. 1(*a*) and (*b*) represents observations of the plasma water and specific gravity made on patients in labour. After 20 hours in labour a state of dehydration developed and this persisted for the remainder of the time the patients were studied. On examination of the patients at this time the clinical signs of dehydration were not found. Observations made a few days postpartum showed that the normal plasma hydration had been restored (Table III). The plasma

specific gravity, however, was high in the puerperium (Table III); this effect is probably due to the rise in plasma proteins which occurs in the weeks after delivery (Coryell *et al.*, 1950).

A small number of observations of the packed cell volume in prolonged labour were also made; these failed to show any significant change from the value in Table II.

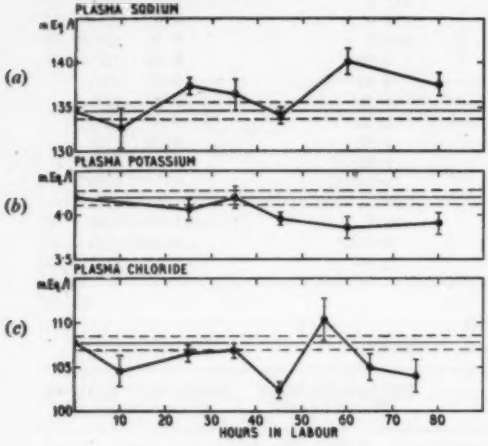

FIG. 2

Plasma sodium, potassium and chloride in prolonged labour.

Plasma Sodium, Potassium and Chloride

In Fig. 2(*a*) it will be seen that in these long labours the plasma sodium tended to rise and after 50 hours the values were markedly elevated. In contrast, after 40 to 50 hours in labour a persistent fall in plasma potassium occurred (Fig. 2(*b*)).

Plasma chloride (Fig. 2(*c*)) fell markedly during the first 20 hours of labour but then recovered. After 40 to 50 hours in labour the values were again low.

Plasma sodium potassium and chloride were also calculated in terms of milli-equivalents per kilogram plasma water. The mean values for the ions expressed in these terms showed changes parallel to those shown in Fig. 2.

Plasma Calcium and Magnesium

During the first 20 hours of labour, plasma calcium was significantly reduced, magnesium

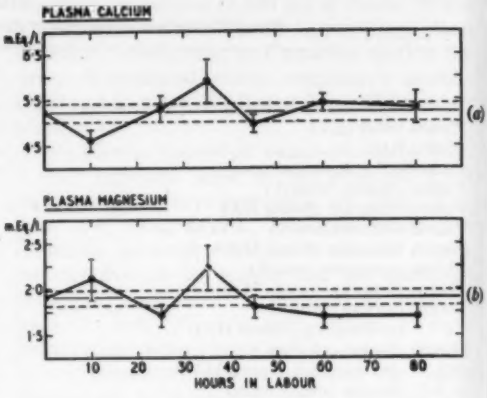

FIG. 3

Plasma calcium and magnesium in prolonged labour.

remaining unchanged. Otherwise the plasma levels of these ions (Fig. 3(*a*) and (*b*)) showed little change in prolonged labour. Values for Ca^{++} and Mg^{++} ions per kilogram plasma water were calculated from the normograms given by McLean and Hastings (1935) and Willis and Sunderman (1952). Expressing the ionic levels in these terms confirmed that there

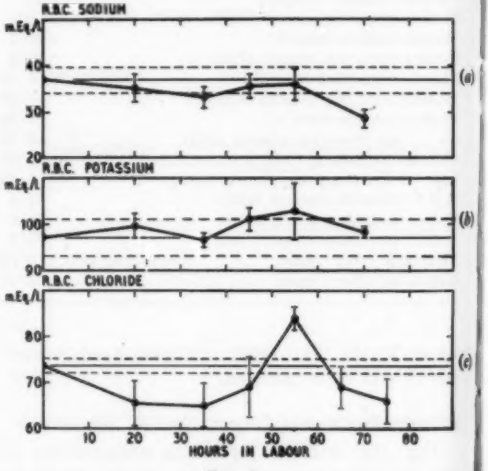

FIG. 4

Red blood cell electrolytes in prolonged labour.

was no significant change in plasma calcium or magnesium, with the exception of the plasma magnesium after 70 to 90 hours in labour, which was significantly lower than the reference value.

Red Blood Cell Electrolytes

We were unable to detect any significant change in red cell sodium or potassium (Fig. 4(*a*) and (*b*)), until 60 to 80 hours after the onset of labour when the red cell sodium fell. Red cell chloride (Fig. 4(*c*)) tended to follow the plasma chloride, falling slightly in prolonged labour. We are inclined to discount the single high mean value for chloride obtained at 50–60 hours, because it corresponds to a similarly aberrant value obtained for plasma chloride at that time (Fig. 2(*c*)).

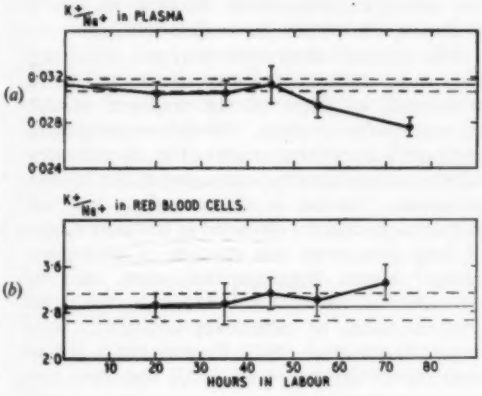

FIG. 5

Potassium/sodium ratios in the plasma and red blood cells in prolonged labour.

Blood Potassium/Sodium Ratios

The course of the plasma potassium/sodium ratio in the long labours studied is shown in Fig. 5(*a*). The ratio was low during the first 20 hours of labour, then rose again to its previous level. After 50 hours in labour a statistically significant fall in the ratio occurred.

The potassium/sodium ratio in the red cells (Fig. 5(*b*)) remained steady up to about 50 hours in labour. Then an apparent rise in the mean value was observed, occurring at approximately the same time as the fall in mean plasma potassium/sodium; this inverse change in the red cells, however, was not statistically significant.

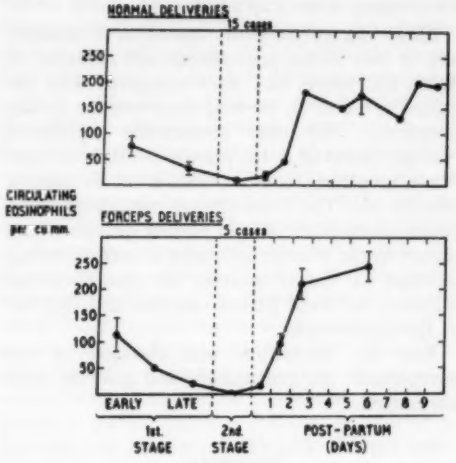

FIG. 6

Circulating eosinophil counts in labour and the puerperium. Standard errors are indicated where sufficient observations are available.

Eosinophil Counts

The observations summarized in Figure 6 demonstrate the marked fall in blood eosinophils which occurs in the course of labour. They confirm the findings of Davis and Hulit (1949) that the circulating eosinophils gradually decrease during the first stage of labour, reaching a minimum in the second stage.

Thorn, Prunty and Forsham (1947), and Hills, Forsham and Finch (1948) found in human subjects that adrenal cortex hypersecretion, induced by the injection of adrenocorticotrophic hormone, produces a similar eosinopaenia. Since then, many forms of physical stress have been found to cause increased adrenal cortex secretion and a consequent fall in circulating eosinophils. The progressive eosinopaenia which occurs in the labouring woman suggests that adrenal cortex secretion increases in response to the stress of labour.

The rise in eosinophil count which takes place in the first few days of the puerperium is also shown in Figure 6. This rise may be due to withdrawal of excess adrenal cortex secretion.

Electrolytes in the Puerperium

Blood electrolyte levels measured in patients one to two weeks post-partum are recorded in Table III. When they were compared with the values in Table II, derived from women in late pregnancy, the only statistically significant changes observed in the plasma electrolytes were a rise in plasma sodium, and a fall in plasma calcium ion. The latter change may simply be a consequence of the rise in plasma protein which occurs in the puerperium, with a corresponding increase in the proportion of protein-bound calcium; the total plasma calcium did not fall in the puerperium.

Red cell potassium was elevated in the puerperium; red cell sodium and chloride were unchanged.

Discussion

The most important of the changes observed in these cases of prolonged labour treated conservatively is the marked fall in plasma water which occurs after about 20 hours. It is of particular interest that this water loss is not necessarily accompanied by the clinical signs of dehydration. Patients found to be dehydrated on examination were of course given parenteral fluids and were removed from the study. The present findings show that women in prolonged labour become dehydrated to a degree which, though not detectable clinically, implies a loss of fluid reserve. Any further loss of fluid or malabsorption can then rapidly produce a severe and dangerous state of dehydration. It would seem desirable, therefore, to give parenteral fluid to every woman who has been in labour 24 hours, unless she is on the verge of delivery, even if signs of dehydration are not present on examination.

The cause of the fall in plasma water may be malabsorption of fluid from the gastro-intestinal tract and vomiting. This possibility is supported by the fact that the plasma chloride is also low in prolonged labour, although sodium rises after the first 20 hours. Another factor which might assist to produce dehydration and chloride loss in the face of sodium retention is the ketosis which often develops in prolonged labour; increased renal excretion of chloride may be required to maintain the body acid-base balance.

During the first 20 hours of labour the plasma chloride was low and there was a coincident though not statistically significant transient fall in plasma sodium. These effects represent a change which occurs between women 39- to 40-weeks pregnant but not in labour, and women in early labour; the changes occurred before the onset of dehydration. They perhaps reflect a loss of salt due to oestrogen withdrawal occurring about the time of the onset of labour. We were unable to deduce from the present data whether this presumed salt loss was initiated shortly before the onset of labour or during the first few hours in labour.

The plasma electrolyte changes occurring after many hours in labour, are most readily interpreted in terms of the response of the adrenal cortex to stress. The fall in circulating eosinophil count that occurs (Fig. 6) indicates adrenal cortex activity, increasing as the labour progresses. The rise in plasma sodium and fall in plasma potassium observed in the later stages of long labour are the changes of prolonged adrenal cortex hypersecretion—they can be reproduced in normal individuals by the daily administration of adrenocorticotrophic hormone (Thorn *et al.*, 1947; Prunty, 1953). It has been shown (Thorn *et al.*, 1953) that both the stress associated with muscular activity and that due to surgical procedures is accompanied by eosinopaenia and increased output of adrenocortical hormones. It seems likely that similar phenomena occur in labour and that the electrolyte changes we observed were a physiological response of the adrenal cortex to the prolonged stress of long labour. It is interesting to note from Figure 5 that after about 50 hours in labour, when the plasma potassium/sodium ratio has fallen markedly, there is some indication of a rise in the red cell potassium/sodium ratio. This was due to a fall in red cell sodium, the potassium level remaining unaltered. MacPhee (1953) found a similar change in the

red cells of patients on the day following surgical operations. Eosinopenia was present at that time, as in the present cases, and it is possible that the effect is due to adrenal cortex secretion.

Csapo (1956) has shown that the tension which uterine muscle can produce in response to a stimulus varies directly, over the physiological range, with the potassium concentration in the surrounding medium, provided the uterus is dominated by oestrogen influence—this he believes to be the case in parturition. Further, the strength of the threshold stimulus required varies inversely with the potassium concentration. That is, the higher the potassium concentration, the smaller the stimulus required to elicit a contraction. Therefore, the fall in plasma potassium seen in Figure 2(*b*) after about 50 hours in labour is almost certainly reflected in the extracellular fluid which surrounds the uterine muscle cells. It is, therefore, likely that this fall in plasma potassium in fact contributes to uterine inertia and further prolongation of the labour with progressively less likelihood of a spontaneous or assisted vaginal delivery.

The findings in the present work suggest certain possibilities in the conservative treatment of labours which are normal in respects other than their length. The dehydration which appears to occur after 24 hours in labour, without necessarily producing clinical signs, indicates a need for the parenteral administration of fluids. The nature of the electrolytes required should be carefully considered, as it is rather difficult to decide which of the changes in the *milieu intérieur* occurring in long labour are in fact physiological adaptation. Simple replacement of all changes might conceivably do more harm than good. It seems unlikely that an attempt to reverse any changes occurring in the first 24 hours of labour would be beneficial. After this time there is little doubt that administration of fluid, glucose and chloride would be of value. It is suggested, therefore, that at this stage a litre of the well-known isotonic preparation containing 4·3 per cent glucose and 0·18 per cent sodium chloride should be given by intravenous infusion.

If it is proposed to allow a patient to continue in labour after 48 hours, it is desirable that biochemical control should be instituted, since, while the present work indicates trends, there is marked individual variation in the changes that occur. Plasma sodium, potassium and chloride should be estimated, preferably on heparinized blood taken with care to avoid haemolysis. Measurement of the plasma water and specific gravity are estimations of considerable value. For treatment, a Ringer solution containing sodium, chloride, potassium and glucose will probably be selected. Particular attention should be paid to the administration of proportionate amounts of potassium, where this ion is low, as a low potassium level may contribute to uterine inertia. The dangers of giving very large amounts of potassium intravenously are well-known, but it is extremely unlikely that any ill-effect could result from giving at the normal rate any of the usual Ringer solutions, containing less than 1·5 grams of potassium chloride per litre. The tendency of the plasma sodium to rise in prolonged labours should be considered, and, with patients whose plasma sodium is markedly elevated, an ammonium chloride Ringer solution, in which part of the sodium chloride is replaced by ammonium chloride, may be given, if the presence of acidosis can be excluded by estimation of the plasma alkali reserve. The quantity and quality of electrolytes that a patient should be given can only be determined after a biochemical analysis of blood and urine. Such an analysis is just as important in prolonged labour as in medical or surgical conditions.

Summary

(1) Blood electrolytes were studied during the course of 29 prolonged labours.

(2) After 24 hours in labour, plasma water fell, and plasma specific gravity rose, although by clinical criteria the patients were not dehydrated.

(3) After 48 hours in labour, plasma sodium rose and plasma potassium fell; plasma chloride was low at this time. These changes are attributed to adrenal cortex hypersecretion. It is suggested that the fall in plasma potassium contributes to uterine inertia and further prolongation of the labour.

(4) Women in labour more than 24 hours should be given parenteral fluid; biochemical control and appropriate replacement therapy with fluid and electrolytes should be instituted in women who have been in labour for 48 hours.

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PREGNANEDIOL EXCRETION IN NORMAL AND ABNORMAL PREGNANCY

BY

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TOGETHER WITH

OBSERVATIONS ON PLACENTAL HISTOLOGY IN NORMAL AND ABNORMAL PREGNANCY

BY

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PART I

PREGNANEDIOL EXCRETION IN NORMAL AND ABNORMAL PREGNANCY*

INTRODUCTION

EVER since it was shown that pregnanediol occurred in quantity in the urine of pregnant women it has been hoped that the estimation of this excretion product would help in the care of patients during the antenatal or intra-partum period. Unfortunately these hopes were not realized, and this was due, in part at least, to serious errors in the method of assay (Coyle, Mitchell, Paine and Russell, 1955). The improved results of assaying pregnanediol by partition chromatography (Coyle, Mitchell and Russell, 1956) justified a re-appraisal of the whole question of pregnanediol excretion levels in abnormal pregnancy. Such is the content and purpose of this paper.

RESULTS

We now give the results of this examination reporting on the pregnanediol excretion in mg. per 24 hours. Studies have been made throughout normal pregnancy, in abnormal early pregnancy, in hydatidiform mole, in toxaemic pregnancy, in pregnancy complicated by essential hypertension and by chronic nephritis, in pregnancy complicated by ante-partum haemorrhage, in pregnancy complicated by diabetes, and in pregnancy complicated by Rhesus incompatibility. Almost all the assays have been the responsibility of one of us (M.G.C.), assisted by Miss M. Early, B.Sc., Research Biochemist, University Department of Obstetrics and Gynaecology, and Mr. Raymond Hall, and the work has been carried out in the laboratories in the Jessop Hospital for Women, and the patients providing the specimens have in general been attending the Jessop Hospital. A small

* The substance of this paper formed the basis of an M.D. thesis (by M.G.C.) accepted by the University of Glasgow.

number of assays have been carried out by Dr. Jordan and his staff at the Royal Infirmary, Sheffield, especially in connexion with cases admitted to the University Clinical Unit, City General Hospital, Sheffield.

The notes of all cases have been carefully reviewed by at least two and usually three of us, and only those in which the diagnosis was reasonably certain have been included. Unless otherwise stated only those values of pregnanediol which preceded foetal death have been reported.

Normal Pregnanediol Excretion

In order to study the general pattern of pregnanediol excretion in normal pregnancy, 24-hourly specimens from 25 patients have been examined; of these patients 12 were primiparae. From 4 to 31 specimens were examined in respect of each patient.

Figure 1 illustrates the average level of pregnanediol excretion throughout the course (10th to 40th week) of pregnancy, together with limits of what may be described as "normal" excretion. Thus, if a normal patient has her pregnanediol excretion measured, say, at the 30th week, it would most commonly be about 36 mg./24 hours, and there would be a 95 per cent chance of it being between 19 and 57 mg. (these figures being given by the lower and upper curves respectively).

It will be observed that the level of pregnanediol excretion tends to rise with gradually increasing rapidity throughout pregnancy until about the 37th week, when it flattens out and falls. Individual records vary a good deal in pattern in the few weeks before delivery (see Appendix, Tables I and II), and, although for clinical application a chart constructed as in Figure 1 is relevant, the possibility was entertained, by constructing a similar diagram working backwards from the date of delivery, that a difference between the diagrams might be apparent such as could give a lead to the

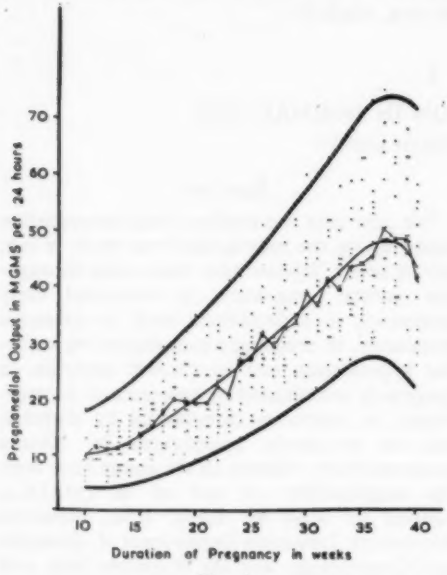

FIG. 1

Scatter diagram of pregnanediol excretion in normal pregnancy (10th to 40th week). Smooth curves have been calculated and drawn to represent the average excretion (fine line) together with the limits of "normal" excretion.

FIG. 2

Smooth curves which have been calculated and drawn to represent the average excretion and the limits of "normal" excretion of pregnanediol during the weeks preceding delivery.

causes underlying the onset of labour. Such a diagram has been prepared (Fig. 2), but no material difference between it and the more orthodox diagram (Fig. 1) is apparent. So it cannot be said that the decline in pregnanediol excretion is any more a sign that labour is likely in a week or so than a sign that chronological "term" is being approached. Accordingly the form of Figure 1 is used throughout this paper. The statistical analysis upon which its acceptance is based is given in the Appendix.

Some care must be used in interpreting individual records in relation to Figure 1. A single isolated observation falling outside the band is certainly indicative of abnormal excretion: if a series of successive observations were made upon a patient, and only one fell outside the band, the rest falling for the most part well within it, the individual's record may still be taken as normal, but if a series of successive observations on the same patient all fall within, but only just within, the limits, this again is indicative of abnormal excretion.

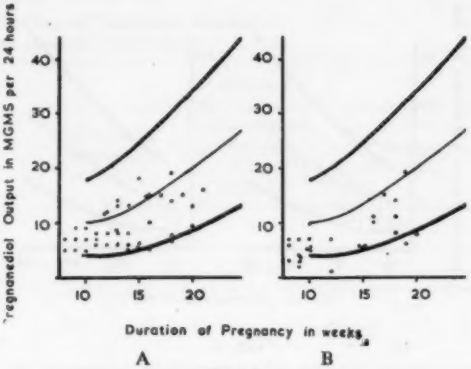

FIG. 3

A.—Scatter diagram of pregnanediol excretion in 41 cases of threatened abortion ending in live births.

B.—Scatter diagram of pregnanediol excretion in 27 cases of threatened abortion ending in abortion.

THE PREGNANEDIOL EXCRETION IN EARLY ABNORMAL PREGNANCY

In this section we report and discuss the pregnanediol excretion of patients who for one reason or another had come under close medical care in early pregnancy. These cases fell into two broad classes, those threatening to abort, and those with a history of previous abortion.

Threatened Abortion

The values for pregnanediol excretion in 68 patients diagnosed as suffering from threatened abortion were available for analysis; of these 41 carried on with their pregnancy to viability and 27 aborted. These two groups were reviewed separately. Scatter diagrams were prepared (Figs. 3A and 3B) using one reading for each case, and taking the one first obtained after the diagnosis was made. Though it is at once apparent from the charts that there is very little to choose between them, two small matters deserve mention. Firstly, very low values, i.e., below 4 mg./24 hours have in our experience been associated with abortion rather than with a continuing pregnancy; this may only mean that occasionally a case of missed abortion is mistakenly diagnosed as threatened abortion. Secondly, normal values after the third month, even with a growing uterus, give no guarantee that abortion will not eventually take place. This is in accord with our clinical experience of patients who abort at the 5th and 6th month.

Reviewing all the evidence, we have reached the firm conclusion that so far as threatened abortion is concerned single estimates of pregnanediol excretion serve little or no useful purpose.

Besides the above study of single readings, 25 patients were more closely studied by repeated assays because it was feared for one reason or another that they would lose their pregnancy. This is an especially heterogenous group of cases because the clinical anxiety in some was based on the previous history whereas in others it was based on events in the pregnancy under review. Repeated assays were made, sometimes even daily and sometimes over many weeks. Of these 25 patients 16 carried the pregnancy to viability and 9 aborted. The pregnanediol values in these two groups have been analyzed to see if the changing pattern of excretion in them was materially different. The values obtained each week in those cases carrying to viability were plotted on a scatter diagram (Fig. 4A) where it may again be noted that no values less

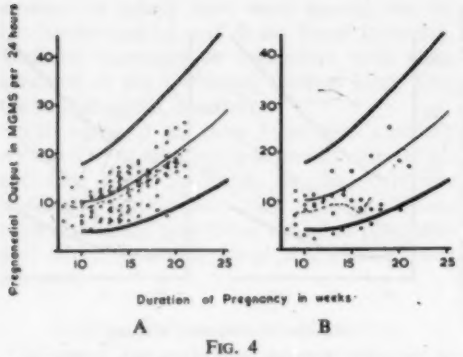

FIG. 4

A.—Scatter diagram of pregnanediol excretion in 16 patients (studied by repeated assays) who carried to foetal viability. The average excretion in this group is shown as a broken line.

B.—Scatter diagram of pregnanediol excretion in 9 patients (studied by repeated assays) who did not carry to foetal viability. The average excretion in this group (only calculated if there were 3 or more values for any one week) is shown as a broken line.

than 4 mg./24 hours were observed. In addition, the average excretion for each week has been calculated and drawn into the diagram as a dotted line, which is at once seen to lie remarkably close to the normal average line—perhaps hardly surprising, as all cases carried at least to 28 weeks.

Only 9 patients who did not carry to viability were available for study, and their values are seen in Figure 4B where the average values (based on 3 or more readings being available) for each week are added as a broken line. Two points deserve mention, the first that a few values below 4 mg. were reported, and the second that from the 12th–17th week there was no rise in average levels compared with that in the cases carrying to viability. Whether either of these slight differences will come to be of any use in the management of early pregnancy remains to be seen; on the whole we think they will not, for there are exceptions. Two of the women who carried to viability showed little or no increase in pregnanediol excretion between the 3rd and 4th month, and one of the women who miscarried showed a good rise in pregnanediol excretion at this time. In regard to the very low values, we believe they mean no more than that a missed abortion has been mistakenly diagnosed as a threatened abortion.

Within the above groups were 7 patients who were given stilboestrol from early pregnancy. Six of these patients delivered living babies at or near term and one aborted at the 24th week. Repeated observations were made, but no difference in the pregnanediol excretion could be detected between cases given stilboestrol and comparable cases without this treatment.

The Conversion of Exogenous Progesterone in Cases of Threatened Abortion

Guterman (1953) maintained that when progesterone was injected intramuscularly in cases of threatened abortion, abortion ensued in those cases where less than 20 per cent of the progesterone was converted into pregnanediol, but if the conversion was above 20 per cent the pregnancy continued. From the following study we have not been able to confirm this work.

Fifteen patients between the 9th and 20th week of pregnancy, threatening to abort, had pregnanediol assays made on three consecutive days after admission. On the 4th day, a quantity (90–100 mg.) of accurately weighed progesterone in 2 ml. sesame oil was injected intramuscularly. The percentage of the progesterone excreted as pregnanediol was then calculated from the pregnanediol excretion during the next 3–4 days. Of this group of 15 patients, 8 aborted and 7 retained the pregnancy (Table I). The conversion rate of progesterone so calculated varied in the abortion group from zero to 29 per cent, and in the live birth group from 2·4 to 30 per cent. The amount of progesterone converted bore no relationship to the urinary pregnanediol levels nor to the duration of pregnancy at the time of injection. The conversion rate was not demonstrably higher or lower in the live birth than in the abortion group.

The Pregnanediol Excretion in Hydatidiform Mole and in Chorionepithelioma

Eight cases of hydatidiform mole were available for study. The pregnanediol levels when the diagnosis was first made are not remarkable, some being normal and others low. The levels after evacuation of the mole (or

TABLE I

The Progesterone Recovery in 15 Cases of Threatened Abortion (Amount of Progesterone Injected, 90–100 mg.)

Live Births			Abortion		
Duration of Pregnancy in Weeks	Pregnanediol Excretion Before Injection	Recovery (Per cent)	Duration of Pregnancy in Weeks	Pregnanediol Excretion Before Injection	Recovery (Per cent)
11	10·8	7·0	9	4·0	29
12	5·5	2·4	10	2·5	17
13	7·5	30·0	11	7·3	6·4
14	17·0	7·0	13	10·7	Nil
16	14·4	11·6	13	3·3	10·9
17	9·0	27·0	16	9·0	5·8
18	7·0	26·0	16	5·0	8·6
			20	10·9	6·3

other appropriate treatment) however show some unusual and interesting features. Whereas in 6 out of the 8 cases the level of excretion was low, in 2 cases (outlined below) it remained raised for some considerable time after evacuation, seemingly because of the continuing presence of theca lutein cysts.

Mrs. S., aged 24. Hospital No. 4645

This gravida-2 presented with vaginal bleeding and pain after 14-weeks amenorrhoea, and had a uterus the size of a 17-weeks pregnancy. No foetal parts were detected, the Aschheim-Zondek reaction was positive, the urine containing gonadotrophic hormones at a level of one million mouse units per litre: the ovaries were enlarged to four times the normal size. The pregnanediol excretion was 26 mg. per 24 hours before evacuation of the mole, 23 mg. per 24 hours the next day, 17 mg. per 24 hours 7 days later, 12·8 mg. per 24 hours after 28 days, 3·2 mg. per 24 hours after 6 weeks, and 0·7 mg. per 24 hours after 10 weeks. The gradual fall in the pregnanediol excretion was roughly parallel to the reduction in the size of the ovaries which a month after evacuation of the mole were still enlarged to twice the normal size, and were slightly enlarged 4 weeks after the evacuation.

Mrs. H., aged 39. Hospital No. 14976

This gravida-6 presented with vaginal bleeding. There was no history of amenorrhoea, but a soft uterus was felt extending almost to the umbilicus. No foetal parts were present. The Aschheim-Zondek was positive with urine diluted 1 in 10, but negative with urine diluted 1 in 100. At laparotomy the ovaries were enlarged to 5 times the normal size by theca lutein cysts. Hysterectomy was performed, and about three-quarters of the total ovarian substance was resected (it was feared that the large ovaries were particularly liable to undergo torsion). In spite of the removal of ovarian substance pregnanediol 8 mg. per 24 hours was excreted 7 days after the operation.

The close relationship we have observed between theca lutein cysts and unusually high levels of pregnanediol excretion is a finding of much interest though its full significance is not yet clear.

In one case of chorionepithelioma the pregnanediol excretion before hysterectomy was 1·5 mg./24 hours.

PREGNANEDIOL EXCRETION IN TOXAEMIC AND HYPERTENSIVE PREGNANCY

In this section the levels of urinary pregnanediol excretion in cases of pre-eclamptic toxaemia, in cases showing essential hypertension in pregnancy, in cases with some combination of a pre-existing hypertension and

pregnancy toxaemia, and in cases of chronic nephritis in pregnancy are examined. It is, of course, well known that these disease processes often so merge into one another that clear-cut diagnosis is impossible; nevertheless some subdivisions seem to us worthwhile. Where the numbers justified it, each group was further subdivided according to whether the outcome of the pregnancy was either a live birth, or a stillbirth or neonatal death.

Essential Hypertension in Pregnancy

We have chosen to include in this group patients whose blood pressure reached 140 systolic and/or 90 diastolic on two occasions, and in whom albumin was never found. Most cases falling into this category and attending the Jessop Hospital for Women had been selected comparatively early in their pregnancies so that in them the diagnosis was fairly certain. Only a few were seen and studied for the first time late in pregnancy, and the diagnosis in them is less certain; the notes of each case have however been carefully reviewed, and we believe their inclusion in this section is reasonable; besides, as will be apparent later, their inclusion makes little or no difference to the general picture.

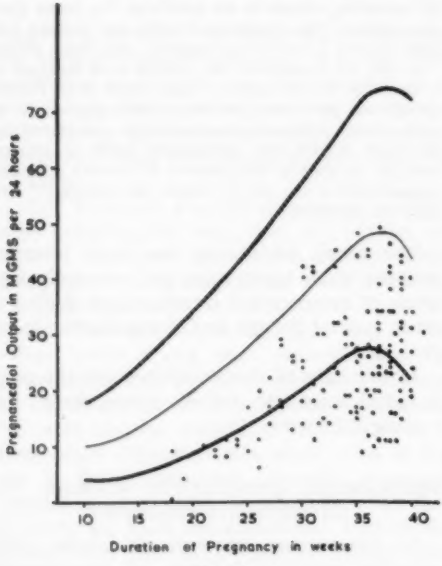

FIG. 5

Scatter diagram of pregnanediol excretion in 19 cases of pregnancy ending in a live birth but complicated by essential hypertension.

First of all 19 women with hypertension alone whose pregnancies ended in a live birth were studied. The results are shown in Figure 5. The striking feature of this graph is that nearly all the individual readings lie below the average normal curve, and many lie below the normal range; assuming pregnanediol excretion is an index of placental function, the general picture is then one of somewhat impaired function. Despite this the babies survived, so it was thought desirable to re-examine the case records of those showing the lowest and highest values of pregnanediol excretion to see whether from these case records there was any evidence to refute the general impression. From this close study it is fair to say that in the cases with the lowest values very special care of the patient had been required in order to get a live child. Rest, sedatives, in one case hypotensive drugs, induction of premature labour, and skilled intra-partum and post-partum care were generally required. One case will serve as illustration.

Mrs. B. No. 14440

This primigravida, aged 42, with a hypertension of the order 160/100 was first seen at the Jessop Hospital for Women, Sheffield, at the 36th week of pregnancy, when a uterus the size of 32–34 weeks was found. She was sure of her dates, and her periods before this pregnancy had been quite regular. She was admitted for rest. At the 37th–38th week of the pregnancy the foetus was judged very small and the clinical diagnosis was probable placental insufficiency; the output of pregnanediol per 24 hours was only 10 mg. on three different occasions. Two weeks later, about the 38th week of her amenorrhoea, artificial rupture of the membranes was carried out because the foetus did not appear to be growing and because the pregnanediol excretion was so low. A small quantity of thick meconium-stained liquor was obtained; in view of this, and after further discussion, lower segment Caesarean section was recommended and performed, when a 4 pounds 1 ounce baby was delivered; the placenta weighed only 14 ounces. Apart from a rather atrophic trophoblast the placental histology was not remarkable.

Another feature of these cases is illustrated in Figure 6 which shows the pregnanediol levels in 4 patients. It will be noted that, whereas in the normal curve there is a steady rise between

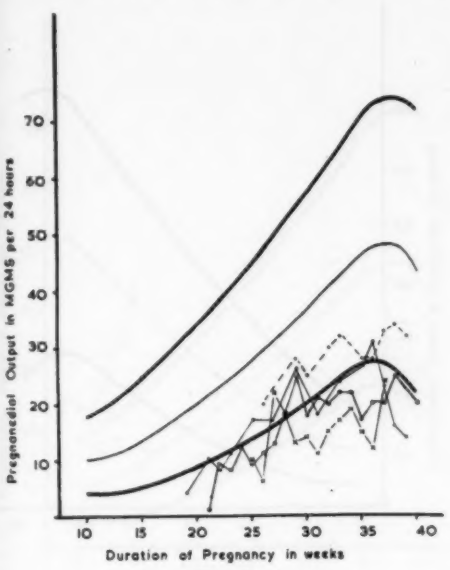

FIG. 6

The pregnanediol excretion in 4 patients whose pregnancy was complicated by essential hypertension.

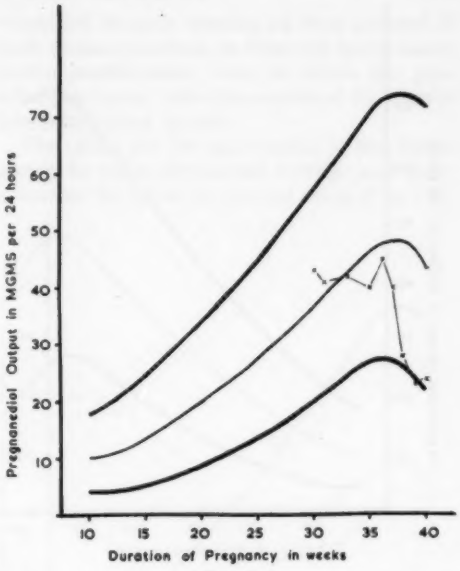

FIG. 7

The pregnanediol excretion in one case of pregnancy complicated by essential hypertension. The excretion in this case was reasonably normal (compare with the more usual excretion in this type of case as illustrated in Fig. 6).

the 5th and the 8th month, in each of the four cases illustrated the curve besides being set much lower is very much flatter.

The cases mainly responsible for the pregnanediol levels above average were also closely reviewed, but no clear difference could be found distinguishing them clinically from the majority who had low values. One case, despite hypertension, showed fairly normal values as is illustrated in Figure 7. It may be that she illustrates the clinical group which so far can only be recognized in retrospect, namely, those with hypertension which does not obviously endanger the foetal life.

Pregnanediol Excretion in Cases of Moderate to Severe Pre-eclampsia

In this section are recorded the values of urinary pregnanediol in mg. per 24 hours in 21 patients with moderate to severe pre-eclampsia. By this we mean patients normotensive in early pregnancy who later showed a substantial rise in blood pressure often up to 160/100 and who passed albumin in considerable quantity in the urine. Eleven cases ending in a live birth were first studied. All babies weighed less than 6 pounds at birth, and most weighed considerably less. Five out of the 11 cases were delivered by Caesarean section, and much skill was required to get a living child. The placentae were small, sometimes weighing less than a pound. It is at once apparent that in this group the pregnanediol levels are usually well below the normal range (Fig. 8).

Urinary pregnanediol levels for 10 cases of severe pre-eclampsia resulting in a stillbirth or neonatal death were also available for study. The values (and only those which preceded the foetal death are charted, Figure 9) are mostly well below the normal range. The case records of two patients who gave values just within the normal range, are reviewed in greater detail.

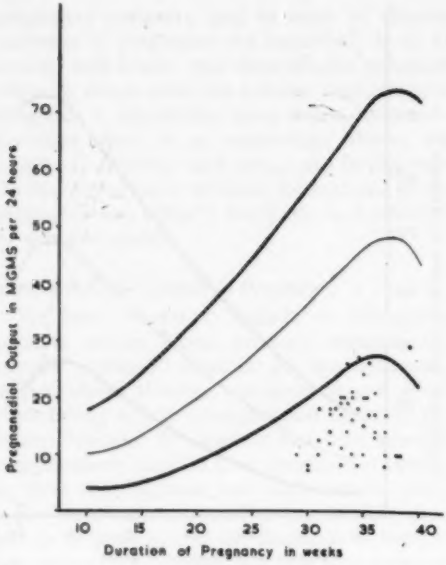

FIG. 8

Scatter diagram of pregnanediol excretion in 11 cases whose pregnancy was complicated by moderate to severe pre-eclampsia.

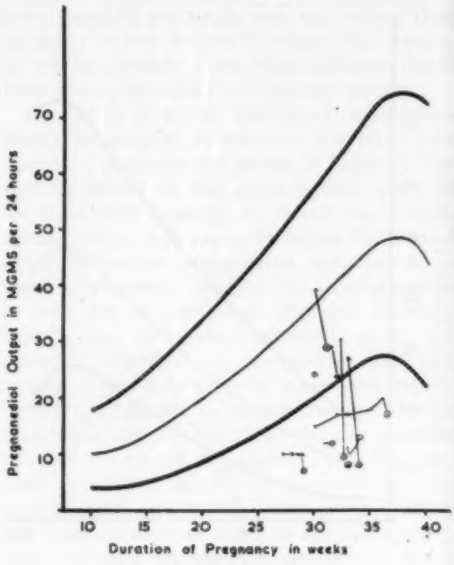

FIG. 9

Pregnanediol levels in 10 patients with moderate to severe pre-eclampsia whose pregnancy ended in a stillbirth or neonatal death. Dots refer to cases ending in stillbirth, crosses those ending in neonatal death: rings mark the last value before death of the baby.

Mrs. B. Hospital No. 13866

This woman, who gave a history of one miscarriage, was aged 42, and was due on the 11th May, 1956. She had severe pre-eclampsia, and on the 7th March a lower segment Caesarean section was performed, and a 3 pounds baby delivered, which subsequently died. In this case, the pregnanediol excretion on the 2nd March was 39 mg. per 24 hours, and on the 5th March, 29 mg. In retrospect it may be questioned whether, with these relatively high values of pregnanediol, the child's interest might better have been served by allowing the pregnancy to continue longer. (On the other hand, so long as the pregnancy continued there was the risk to the mother to be considered.)

Mrs. K. Hospital No. 6679

This primigravida, aged 39 years was due on the 19th June, and had very severe pre-eclampsia developing into eclampsia just before her delivery. A day or so before the delivery of her stillborn child the pregnanediol excretion was 24 mg. per 24 hours, which did not seem low enough by itself to account for the death of the child; possibly it was the convulsions with the associated maternal anoxia which finally killed the baby.

Mild to Moderate Toxaemia

This group comprises women who were normotensive in early pregnancy but who later developed some slight rise of blood pressure, oedema, or albuminuria insufficient to cause much alarm about the mother's health but usually sufficient to warrant induction of labour before or at term.

A considerable number of assays were available for study in this group of 14 patients and the results (Fig. 10) are very much what might have been expected. Most values were centred below the normal average but still within the normal range; a few were situated well above or well below the others. For example, 6 of the 7 values above the normal average were contributed by one woman who was carrying twins and who had a very mild late pregnancy toxaemia; her babies were born alive and weighed 6 pounds and 5 pounds 13 ounces. The remaining value placed above the normal

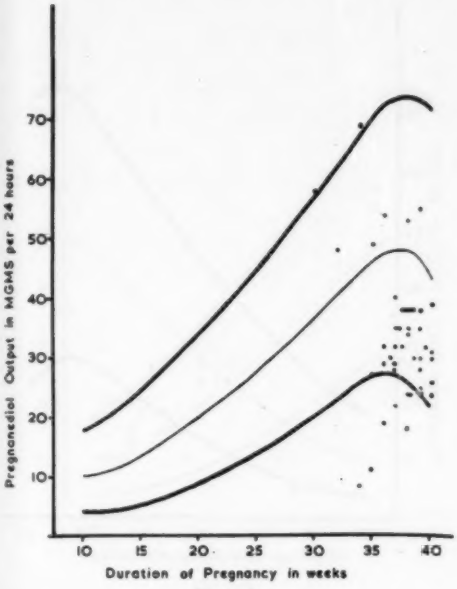

FIG. 10

Scatter diagram of pregnanediol values in 14 patients with mild to moderate pre-eclampsia. All pregnancies ended in live births.

average was contributed by a patient again with a very mild toxaemia who was eventually delivered of a baby weighing 9 pounds 4 ounces. In both these cases, therefore, as judged by foetal size and pregnanediol output, placental function was good.

The two very low values were contributed by a patient whose case was very complicated in that her "pre-eclampsia" developed in her 6th pregnancy, the previous 5 having been normal; there was no rise in blood pressure, only albuminuria and oedema, there were various other complications including obesity, thrombophlebitis, and placenta praevia. The placenta was infarcted. Though we have classified this as mild to moderate toxaemia, our assessment may not be right.

Hypertension and Super-added Toxaemia

This group of patients is rather more heterogenous than the previous ones we have examined, because, whereas all show features of both disease processes, in some the hypertensive factor predominates, and in others the pre-eclamptic factor; also the severity of the disease processes varied greatly.

The values for 14 cases ending in live births mostly lie below the normal average, and quite a number lie below the normal range (Fig. 11);

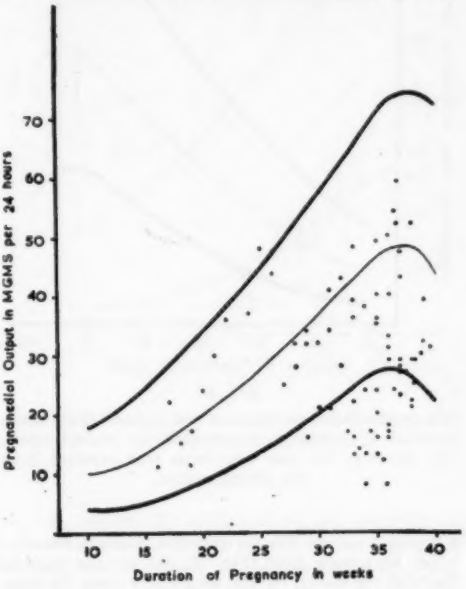

FIG. 11

Scatter diagram of pregnanediol values in 14 cases of essential hypertension complicated by pre-eclampsia.

this is very much what one would have expected to find judging from the charts of hypertension (Fig. 5) and of pre-eclamptic toxaemia (Figs. 8 and 10) taken separately. The very high and very low values deserve close study, especially when the levels of pregnanediol excretion do not always run parallel to the clinical picture. Two cases will serve as illustration.

Mrs. W., aged 21. Primigravida. Hospital No. 11072

This woman was under observation from quite early in pregnancy on account of hypertension of the order 160/100. Toxaemia supervened with albuminuria, and and she was in hospital for some weeks. The membranes were ruptured about the 36th week of the pregnancy and she was delivered the same day of a living child weighing

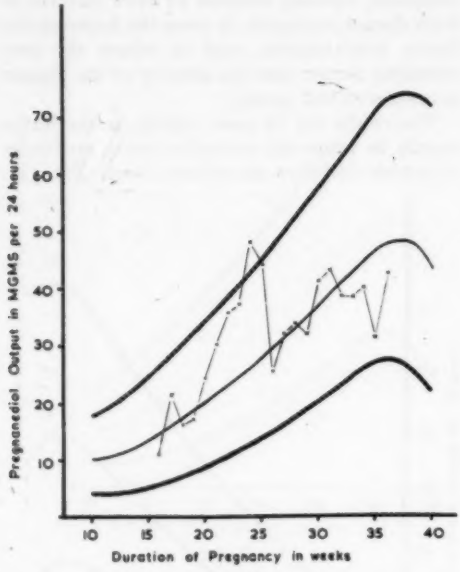

FIG. 12

The pregnanediol excretion in one case of quite severe essential hypertension complicated by pre-eclampsia. The values in this case were better than expected from the clinical picture.

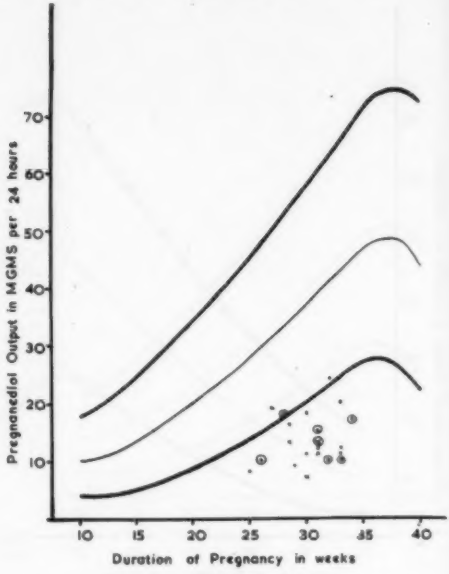

FIG. 13

Scatter diagram of 7 cases of essential hypertension complicated by pre-eclampsia and ending in stillbirth or neonatal death. Dots refer to those cases ending in stillbirth, crosses to those ending in neonatal death: rings mark the last value before the death of the baby.

6 pounds 3 ounces. The pregnanediol values in this case, which were quite good (Fig. 12) did not run quite in line with the clinical picture, which gave cause for some alarm, a fact which of course may be interpreted either as meaning the clinical assessment was too pessimistic or that reasonably high pregnanediol values do not overrule the clinical picture.

In contrast:

Mrs. O., aged 32. Gravida-2. Hospital No. 12192

This woman with a history of eclampsia in her previous pregnancy had a combination of pre-eclamptic toxaemia with oedema and albumin, both disappearing with bed rest, and hypertension of the order 150/90. The disease processes were clinically of like severity to those of Mrs. W. above, yet in Mrs. O.'s case the pregnanediol excretion about the 36th week was alarmingly low, being recorded as 12 mg., 8 mg., and 18 mg. at 2-day intervals.

Only 8 cases showing hypertension and toxaemia and ending in stillbirths or neonatal deaths are available for study. The pregnanediol values obtained shortly before the foetal death are recorded and they are nearly all below the normal range (Fig. 13). The record of one case (Mrs. D.) studied over many weeks is charted separately (Fig. 14).

Mrs. D., aged 34. Primigravida. Hospital No. 11131

Last menstrual period, 24th June, 1955. Expected date of delivery, 4th April, 1956.

This patient first attended at the 10th week of her pregnancy when her B.P. was 165/120 mm. Hg. She attended the antenatal clinic regularly and at the 22nd week of her pregnancy (23rd November, 1956) her B.P. was 190/124 mm. Hg and there was some commencing oedema of legs and ankles. Later she was admitted to hospital with a marked oedema and albuminuria which, at the 26th week of her pregnancy, was up to 8 g. per litre. The foetal heart was not heard on the 23rd December, marked with an arrow on the chart, but it is not certain how long the foetus had been dead. Eventually, on the 3rd January, at the 30th week, she was delivered of a macerated stillbirth weighing 1 pound 4 ounces. The placenta, which was very infarcted, weighed only 6¼ ounces. Nine months after delivery there was no albuminuria, and the blood pressure was still 165/120.

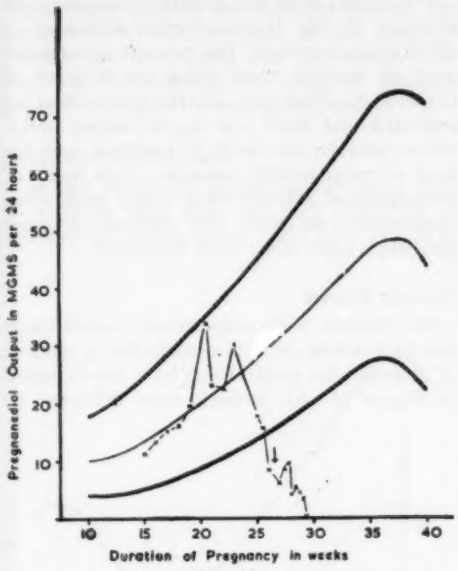

FIG. 14

The pregnanediol values in one case of essential hypertension complicated by pre-eclampsia and ending in a stillbirth. The approximate time of foetal death is marked with an arrow.

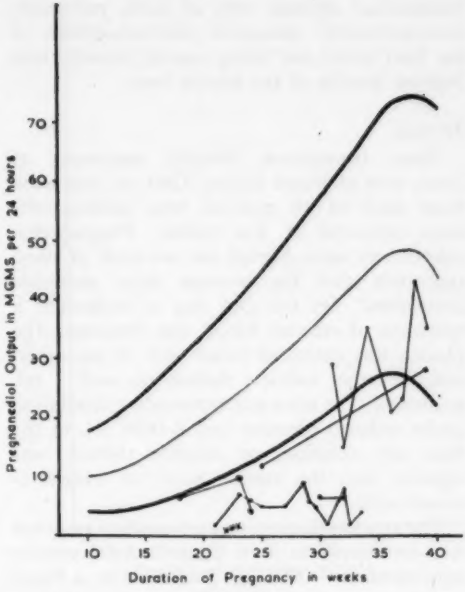

FIG. 15

Pregnanediol values in 6 cases of pregnancy complicated by chronic nephritis.

Pregnancy Complicated by Chronic Nephritis

Cases of pregnancy complicated by chronic nephritis are rare, but 6 such cases have been observed. The values for pregnanediol estimations have been charted in respect of each patient (Fig. 15). In 4 of the cases, despite bed rest, the blood pressure rose, there was heavy albuminuria, and kidney function tests showed gross impairment in concentrating powers; the pregnancies were terminated between 23rd and 34th week. In these cases, pregnanediol values never rose above 10 mg. per 24 hours, and the form of the curves was flat. In the other 2 cases, which were allowed to proceed to term, rest in bed and careful control resulted in some fall in blood pressure, and the degree of albuminuria was never high. In these two cases the level of pregnanediol excretion approximates to the low level of normal, and on the whole the curves show rising values.

In chronic nephritis the severity of the disease is not necessarily reflected in the amount of albuminuria. In this small series the degree of albuminuria appears to be related inversely to the level of pregnanediol excretion, and it is possible that the renal deficiency producing the albuminuria is also concerned in anomalies of pregnanediol excretion.

Progestational Activity of the Blood and Urinary Pregnanediol Excretion

Because it was possible that low levels of pregnanediol excretion might be the result partly or in whole of a renal failure of excretion rather than a low placental output of progesterone it seemed desirable to attempt to estimate progestational activity in blood. The method of Corner and Allen (1929) using rabbits was impractical for multiple tests, and it was decided to adopt the method of Hooker and Forbes (1947). The test depends essentially upon the demonstration of changes in the

endometrial stromal cells of mice, previously ovariectomized, measured micro-quantities of the fluid under test being injected directly into isolated lengths of the uterine horn.

Method

Three consecutive 24-hour specimens of urine were collected during 32nd to 36th week from each of 10 patients who subsequently were delivered of live babies. Pregnanediol estimations were carried out on each of these specimens and the average daily excretion determined. On the 2nd day of collection a specimen of citrated blood was obtained. The plasma was extracted twice with 10 ml. ether, and the ether extracts shaken up with 2 ml. sesame oil. The ether was removed by distillation under reduced pressure and 0·0006 ml. of the final oily solution, or dilution thereof, was injected into the uterine horns of ovariectomized mice.

The greatest dilution giving a positive response was considered to show progestational activity equivalent to 0·0002 μg. progesterone, a figure previously determined by the injection of dilutions of pure progesterone in sesame oil into a control series of mice. The activity of the plasma was then expressed in terms of micrograms progesterone per ml. No attempt was made to hydrolyze the plasma extract, and therefore the recorded figures are an expression of free progestational activity, and do not take into account any conjugated or protein bound progestins. The results in the 10 cases are set out in Table II.

TABLE II

Case No.	Final Duration of Pregnancy in Weeks	Duration at Time of Estimation in Weeks	Average Pregnanediol Excretion in mg. per 24 hours	Progestational Activity in μg. Progesterone per ml.
1	41	34	26·2	3·4–8·5
2	38	35	26·6	> 8·5
3	40	33	27·5	3·4–8·5
4	40	35	32·2	3·4–8·5
5	39	36	36·5	0·9–1·7
6	41	34	37·3	0·2–0·9
7	40	34	39·3	0·2–0·9
8	41	32	42·1	> 8·5
9	40	35	48·0	0·9–1·7
10	40	34	52·0	1·7–3·4

The results show that positive responses were obtained by the Hooker-Forbes technique in all 10 cases examined. The patients investigated were all normal, there being no evidence of impaired renal function, and the results obtained indicated that there was no immediate correlation between the level of response and the level of pregnanediol excretion, high levels of progestational activity being found both when pregnanediol excretion was relatively low and also when high values were registered.

Placenta Praevia

Six patients with ante-partum haemorrhage due to placenta praevia contributed a number of pregnanediol levels which have been charted in Figure 16. All patients were delivered by

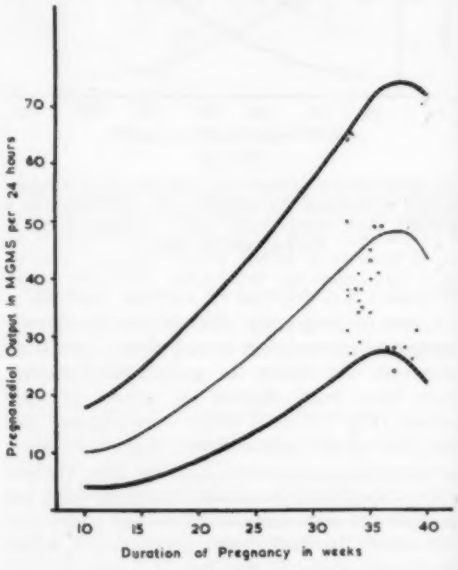

FIG. 16

Scatter diagram of pregnanediol values in 6 cases of placenta praevia. All babies survived except one which died in the neonatal period; the values in this case are marked with circles.

Caesarean section and all babies survived birth though one died in the neonatal period. The values for the live births in all cases fell within the normal range: the only reading below the normal range was the last one of the woman

whose baby died in the neonatal period. The comparatively normal values in this group of patients are in keeping with the clinical view that the haemorrhage in cases of placenta praevia is largely of mechanical origin.

Accidental Haemorrhage

In this group the pregnanediol values from 13 patients have been recorded according to whether the outcome was a live birth (Fig. 17),

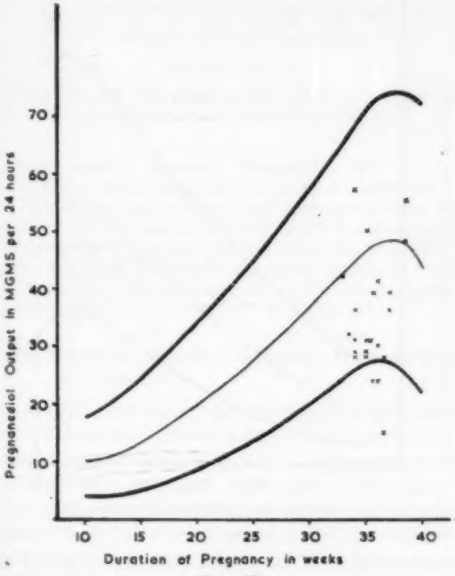

FIG. 17

Scatter diagram of pregnanediol values in 7 cases of accidental haemorrhage ending in live birth.

or a stillbirth or neonatal death (Fig. 18). Though the ante-partum haemorrhage in each case was the presenting sign the group is otherwise rather heterogenous—for sometimes there was some underlying pre-eclampsia or hypertension (or both), and at other times no other complication. Also the severity of the placental separation whether estimated before or after delivery varied greatly.

In the group (7 cases) ending in a live birth the values varied greatly though most fell within the normal range. By contrast, the values

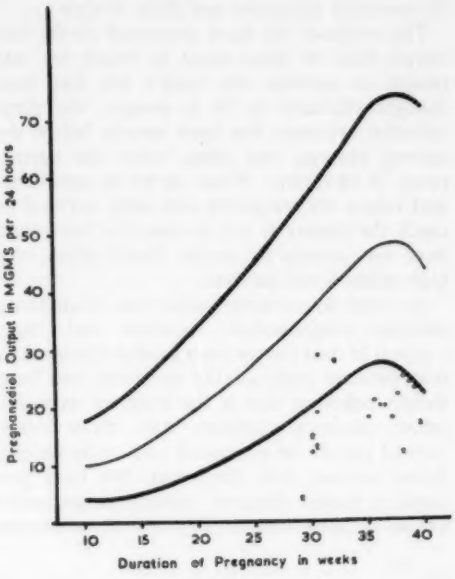

FIG. 18

Scatter diagram of pregnanediol values in 6 cases of accidental haemorrhage ending in stillbirth or neonatal death. The last values before the death of the foetus or newborn have been underlined.

for those cases ending in a stillbirth or neonatal death (6 cases) were mostly well below the normal range: indeed the foetus seldom lived *in utero* for more than a day or so when the pregnanediol values were really low. The following case illustrates the dangers of treating expectantly even the mild case of accidental haemorrhage.

Mrs. McD., aged 27. Gravida-3. Hospital No. 6131

This woman suffered a mild ante-partum haemorrhage about the 34th week of pregnancy and was admitted to hospital. About the 38th week of pregnancy when bleeding had ceased for some time she was examined vaginally. No bleeding or placenta praevia was found so she was allowed home, only to have a stillbirth at home two days later. (Her doctor reported a retro-placental clot.) In this case the pregnanediol values were on the low side, varying over 10 readings between 17 mg. and 25 mg. per 24 hours, and we think not only that artificial rupture of the membranes should have been performed, but that it should have been carried out about 35–37 weeks.

Pregnanediol Excretion and Baby Weight

The evidence we have presented so far has shown that, in those cases in which for one reason or another the baby's life has been thought clinically to be in danger, the pregnanediol excretion has been usually below the normal average, and often below the normal range of excretion. When, however, pregnanediol values are compared with baby survival or death the picture is not so clear for low values have not necessarily meant foetal death, nor high values foetal survival.

In order to examine further the relationship between pregnanediol excretion and likely survival of the baby we have studied the relationship between pregnanediol excretion and baby weight believing that if the levels of excretion reflect placental function then those below normal should be associated with baby weights below normal, and vice versa. We have prepared a scatter diagram relating pregnanediol values to baby weight (Fig. 19). To overcome

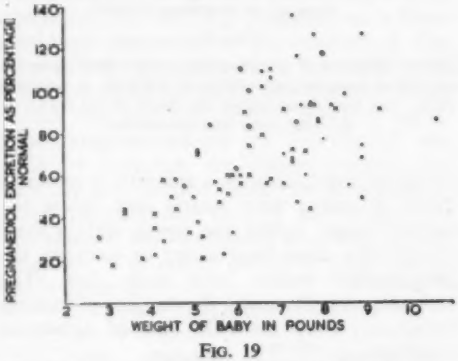

FIG. 19

Scatter diagram of baby weight plotted against pregnanediol excretion (expressed as a percentage of the normal average excretion for the particular period of gestation). Crosses refer to cases of pre-eclampsia and/or hypertension, circles to cases of ante-partum haemorrhage, and dots to normal cases. The approximate linear relationship between baby weight and percentage normal pregnanediol excretion is seen.

variations in pregnanediol excretion at the different gestation periods we have expressed the values as a percentage of the normal average excretion for the particular period of gestation. From this diagram it will be seen that the relationship between baby weight and pregnanediol excretion is approximately linear.

Pregnancy Complicated by Diabetes

Of the 23 patients in this category who have been studied 18 gave birth to babies who survived, 5 had stillbirths or neonatal deaths. The pregnanediol values for all cases have been charted in Figure 20, the values for live births

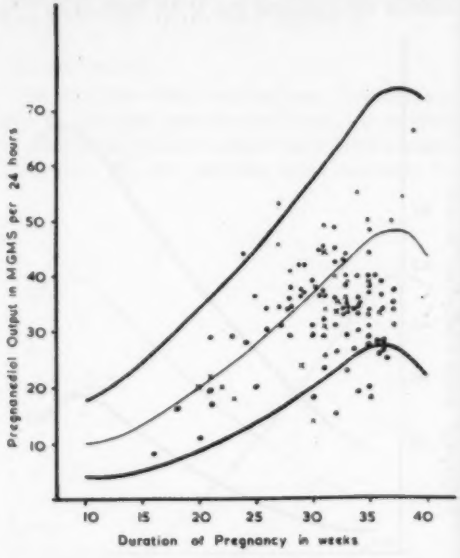

FIG. 20

Scatter diagram of pregnanediol levels of excretion in pregnancy complicated by diabetes. The values for 18 cases ending in live birth are marked with a dot: those for 5 cases ending in stillbirth or neonatal death with a cross.

being marked as dots, and those for stillbirths or neonatal deaths as crosses. It will be seen that the pattern of excretion is very similar to that seen in normal pregnancy and no striking difference is apparent between the live birth group and the stillbirth and neonatal death group. An interesting observation is that on a number of occasions the level of excretion remained up for some time after the foetal death, suggesting that this was not due to placental failure. One case will serve as illustration (Fig. 21).

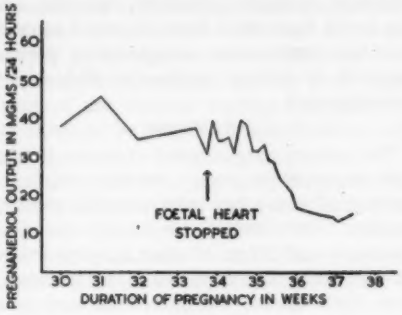

FIG. 21

Chart showing how pregnanediol values can remain up even though foetal death has occurred.

Mrs. P., aged 27. Gravida-2. Hospital No. 7007

Previous intra-uterine death at the 36th week.

This woman had suffered from moderate diabetes for 5 years. She was due on the 4th June, 1955, and repeated pregnanediol assays were made between the 28th March and 19th April. The levels were quite normal to begin with, and even after the baby died at the 33rd week they remained well up for nearly 10 days (Fig. 21).

Pregnancy in Rhesus Negative Women with Antibodies

Studies have been made during 20 pregnancies of 19 Rhesus-negative women with antibodies. In this group there is rather a high proportion of stillbirths (8 cases) and neonatal deaths (1 case), because of some selection on our part of cases likely to have an unsuccessful outcome to the pregnancy. Nine of the living children were affected; two were unaffected, both being Rhesus-Negative. A scatter diagram (Fig. 22) has been prepared of all the pregnanediol values during foetal life, the values in cases in which the baby survived being marked with a dot, those in cases ending in stillbirths or neonatal deaths with a cross. The general picture associated with live births is of normal levels of excretion. That in association with stillbirths and neonatal deaths is of values on the low side of normal, or even in one or two cases of levels just below the normal range. Other factors (e.g., hypertension and placental infarction) contributed to some of these low readings so we do not think low levels of excretion reflect the severity of the Rhesus sensitization; at the same time levels of excretion well below average probably mean that the foetus is in extra danger. Levels of excretion above average seem to carry a better prospect for a viable child, but of course even with such levels the child when it is born will still need treatment: in this series nearly all the affected babies required transfusion.

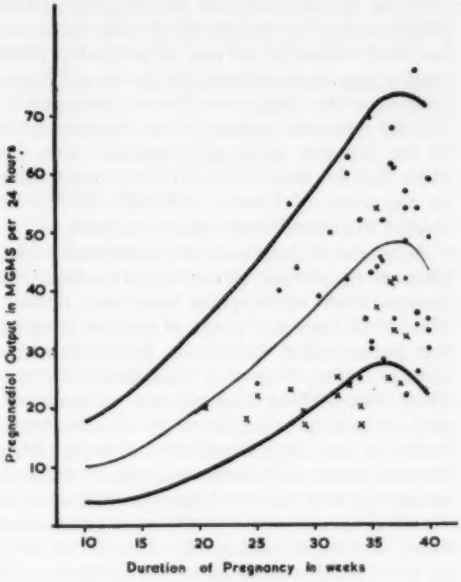

FIG. 22

Scatter diagram of pregnanediol levels of excretion in Rhesus negative women showing antibodies. Cases ending in live birth are marked with a dot: those ending in stillbirth or neonatal death are marked with a cross.

DISCUSSION

In this paper we have made the assumption that the level of pregnanediol excretion in pregnancy is a measure of the normality of at least one aspect of placental function, the validity of this assumption being supported by the fact that baby weight and pregnanediol excretion show roughly a linear relationship. We have examined the levels of excretion in many normal and abnormal cases to try to determine to what extent this assay is likely to prove of value in clinical practice.

Using the new method of assaying urinary pregnanediol, the pattern in normal pregnancy has been shown to be one of a steadily rising level of excretion until the last few weeks before term when the rising curve flattens out and falls. Careful statistical analysis of the excretion levels in the last few weeks of pregnancy does not show that this decline has any direct relationship to the onset of labour; certainly there is no sudden fall immediately prior to labour.

In abnormal pregnancy or in pregnancy complicated by disease certain vagaries from the normal levels of excretion have been noticed. First of all there is a group of diseases in which the pregnanediol levels are generally within normal limits. Pregnancy complicated by diabetes, but without hypertension or toxaemia, and pregnancy complicated by rhesus incompatibility are two conditions showing fairly normal levels of excretion, evidence which is in keeping with the very large placentae so often found in these conditions. Placenta praevia is a third. In these conditions the assay is not likely to be of much assistance to the clinician in his management of the case, unless abnormally low values are found. Likewise, from our experience the assay will not often help in the management of early pregnancy abnormality.

In contrast, the assay in our experience can be helpful in the management of some cases of pregnancy complicated by hypertension, in pre-eclampsia, in pregnancy complicated by nephritis and in accidental haemorrhage. It may be helpful in one of two ways. On the one hand, very low values, by their warning that placental function may be seriously impaired, draw attention to those cases in whom close attention is required: and on the other hand, high values with their reassurance that placental function at least in one respect is good, may encourage a more conservative approach than might otherwise have been contemplated.

A word of warning is necessary lest very low values of pregnanediol output be interpreted as always meaning wholely inadequate placental function; if there is a heavy albuminuria the very low values often obtained may reflect some impairment of renal as well as placental function. In the absence of heavy albuminuria we believe the low levels reflect impairment of placental function primarily, because similar low levels have often been observed in cases of essential hypertension complicating pregnancy in which the kidney function by all known tests is unimpaired.

Summary

The urinary pregnanediol excretion in normal and abnormal pregnancy has been studied. The method of assay has been partition chromatography. For normal pregnancy the average excretion and limits of what may be described as "normal" excretion have been calculated and curves drawn. The curves rise steadily until about the eighth month when they flatten out and fall.

No difference has been found in the curves of normal excretion between those calculated on a basis of weeks of gestation and those calculated on a basis of weeks before delivery.

In threatened abortion the pregnanediol excretion has been closely examined and the levels compared in those cases aborting and those cases carrying to viability: only small differences were observed. The conversion of exogenous progesterone in threatened abortion has also been studied. The conversion rate was not demonstrably higher or lower in the group of patients who aborted than in those who carried to viability.

The pregnanediol excretion in hydatidiform mole has been reported; a relationship between theca-lutein ovarian cysts and a continuing excretion of pregnanediol has been noted.

In pregnancy complicated by essential hypertension the pregnanediol excretion is usually below the normal average and sometimes below the normal range.

In moderate to severe pre-eclampsia the excretion was below the normal range; in less severe cases higher levels were found.

In essential hypertension with superimposed pre-eclampsia variable levels of excretion mostly below the normal average were found.

In chronic nephritis very low levels were found in severe cases.

The progestational activity of the blood has also been estimated and related to pregnanediol excretion: no immediate correlation was found.

In placenta praevia normal levels of pregnanediol excretion were found.

In accidental haemorrhage fairly normal levels were found in association with live births and low levels in association with stillbirths.

Pregnanediol excretion (expressed as a percentage of the normal average excretion) has been shown to be roughly proportional to baby weight.

In diabetes normal levels of excretion were found regardless of the foetal outcome. Pregnanediol excretion has sometimes continued after foetal death, suggesting that in some cases the cause of death was not placental insufficiency. In Rhesus-negative women with antibodies normal levels of excretion have been found with babies severely affected. Reduced levels of excretion have been found preceding foetal death.

Conclusion

The assay of urinary pregnanediol excretion, if carefully and accurately performed, is helpful in the management of some late pregnancy disorders: it may also prove to be a useful measure of the effectiveness or otherwise of new methods of treatment.

We wish to thank our colleagues, Mr. L. B. Patrick, Mr. D. H. Lees, Mr. T. Smith, and Dr. W. J. Clancy, for allowing us access to patients under their care; and Dr. F. L. Mitchell for his supervision of the biochemical work. We also thank Miss Gibson and Dr. G. H. Jowett of the Department of Statistics in the University of Sheffield for the careful and detailed analysis of the pregnanediol excretion in normal pregnancy from which the normal curve of excretion was prepared. We acknowledge help received from Dr. P. M. Wray and Dr. D. H. Blakey, and other members of the medical and nursing staff. The continuing financial support of the Board of Governors of the United Sheffield Hospitals, which we gratefully acknowledge, has made this work possible.

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Appendix

Statistical Analysis

The observations on which the curve of Figure 1 was based were obtained from 25 patients, who contributed numbers of points varying from 4 to 31, successive observations from the same patient tending to be somewhat similar. The curve was fitted by calculating averages at each week, as indicated by the crosses in Figure 7, and smoothing the resulting graph by means of a weighted moving average, with least squares fitting at the ends,* the weights being calculated on the very adequate assumption that over every 13 successive points the curve was approximately representable by a cubic polynomial. The variation of the points above and below the smooth curve was then studied, and the 2·5 and 97·5 percentiles of the distribution of deviations were evaluated. These were then adjusted to the appropriate phase of pregnancy (the standard deviation from the curve was found to increase approximately uniformly with time, from 3·4 units at the 10th week to 12·5 units at the 40th week) and used to locate the upper and lower curves.

It was considered that the existence of the apparent decline in average pregnanediol excretion during the last few weeks of pregnancy should be firmly established by critical and objective statistical analysis. Unfortunately, the data in Figure 1 do not lend themselves to precise statistical tests of significance. Accordingly, for this specific purpose, a separate analysis was carried out on a number of cases (13) for which effectively complete records were available for the eight weeks immediately prior to delivery.

The data for these 13 cases are shown in Table I. A few isolated observations were

* Averages for 41st and 42nd weeks were not taken into account in the curve fitting, since they were based on very few observations.

TABLE I

Data of 13 Patients with Effectively Complete Records for Delivery and the Eight Preceding Weeks

Week	0	1	2	3	4	5	6	7	8
Patient									
1	32	41	43	40	35	42	45	52	37
2	41	41	48	47	48	57	59	47	42
3	30	38	38	39	31	30	27	34	19
4	38	49	*47*	45	*44*	43	*38*	33	*33*
5	58	63	66	59	*51*	43	37	44	31
6	47	49	38	37	32	36	36	27	31
7	40	55	*59*	63	75	73	63	54	45
8	35	46	56	69	54	*46*	38	*34*	31
9	50	42	48	44	48	48	43	46	34
10	33	33	32	46	46	38	30	30	43
11	26	42	37	45	42	34	35	32	*32*
12	59	62	66	55	54	59	58	*58*	*58*
13	51	63	69	64	*64*	63	68	*66*	63

Numbers in italics are interpolated values.

missing; these were interpolated between the values on either side, and an adjustment was made to subsequent analysis to take account of this. An analysis of the variance of these data, shown in Table III, confirms both the existence of differences, in level of excretion, from patient to patient, and of a definite pattern of average excretion over the last eight weeks and also provides the basis for a test of significance of the decline, details of which are shown at the foot of Table III and establish that the decline is significant on the 5 per cent level. (Note: In designing a test for this purpose there was the complication that the decline in the curve had been actually suggested by the apparent decline in means in the data, and a test of significance which ignored this would tend to overstate its statistical significance. This should be assessed by considering the decline in relation to a reference set consisting, not of all possible configurations of values such as might occur fortuitously, but only of the subset of descending configurations; in other words, it should be tested for significance in

TABLE II

Data of 13 Patients with Effectively Complete Records for the 32nd to 40th Weeks of Pregnancy

Week	32	33	34	35	36	37	38	39	40
Patient									
1	52	45	42	35	40	43	41	32	*32*
2	33	42	47	59	57	48	47	48	41
3	49	34	27	30	31	39	38	38	30
4	*33*	33	*38*	43	*44*	45	*47*	49	48
5	31	44	37	43	*51*	59	66	63	58
6	31	27	36	36	32	37	38	49	47
7	37	45	54	63	73	75	63	*59*	55
8	31	*34*	38	*46*	54	69	56	46	35
9	34	34	46	43	48	48	44	48	42
10	40	40	43	30	30	38	46	46	32
11	*32*	32	35	34	42	45	37	42	26
12	*58*	58	59	54	55	66	62	59	59
13	63	*66*	68	63	*64*	64	69	63	51

Numbers in italics are interpolated values.

comparison only with such *declines* as might occur by chance. A simple and appropriate way of doing this is to test merely the *variance* of the last four means before delivery, using the F-test, against an expected value deduced from the interaction mean square (in Table III).)

A parallel analysis was done on observations for the 32nd to 40th weeks (Tables II and IV) and gives a similar result; the decline is actually more significant when tested from this point of view. If it were evidence of the imminence of labour, a less noticeable decline would have been expected in this second analysis, since, in some patients delivered later than the end of this period, the decline would have tended not to start until late during the period. Hence on these data the decline cannot itself be taken as being any more indicative of the imminence of labour than the approach of the chronological full-term.

TABLE III

Analysis of Variance on Data of Table I

Source of variation	d.f.	s.sq.	m.sq.	F
Between patients	12	9,731	811	13·5***
Between weeks	8	1,322	165	2·74**
Interaction	83	4,993	60·2	
Total	103	16,046		

Variance of the means for the four weeks prior to delivery estimated from the means themselves:

$$= \Sigma (\bar{x}-\bar{\bar{x}})^2/3 = 16{\cdot}26 \text{ (3 d.f.)}$$

Expected value from interaction: $= 60{\cdot}2/13 = 4{\cdot}631$ (83 d.f.)

$$F = 16{\cdot}26/4{\cdot}631 = 3{\cdot}511^*$$

* significant at 5 per cent level.
** significant at 1 per cent level.
*** significant at 0·1 per cent level.

TABLE IV

Analysis of Variance on Data of Table II

Source of variation	d.f.	s.sq.	m.sq.	F
Between patients	12	9,539	795	13·9***
Between weeks	8	1,920	240	4·21***
Interaction	83	4,739	57·0	
Total	103	16,198		

Variance of the means for the 37th to 40th weeks estimated from the means themselves:

$$= \Sigma (\bar{x}-\bar{\bar{x}})^2/3 = 19{\cdot}51 \text{ (3 d.f.)}$$

Expected value from interaction: $= 57{\cdot}0/13 = 4{\cdot}385$ (83 d.f.)

$$F = 19{\cdot}51/4{\cdot}385 = 4{\cdot}449^{**}$$

* significant at 5 per cent level.
** significant at 1 per cent level.
*** significant at 0·1 per cent level.

PART II

OBSERVATIONS ON PLACENTAL HISTOLOGY IN NORMAL AND ABNORMAL PREGNANCY

THE placenta during its relatively short life span subserves a wide range of functions. In brief, these may be considered under three headings, the synthesis particularly in early pregnancy of metabolites essential to foetal survival and growth, the elaboration of hormones concerned mainly with the maintenance of pregnancy and the provision at the placental barrier of simple gaseous and metabolite exchange.

ANCHORAGE OF CONCEPTUS

In the first few weeks following conception, activity is directed mainly towards the establishment of a close relationship whereby the trophoblast, probably by cytolytic enzyme production (Hertig and Rock, 1941) anchors itself within the decidua and ensures its own survival. This process is followed speedily by the outgrowth of extra-embryonic mesoderm into the plastic trophoblast shell, and the establishment of a foetal circulation, whereby the nutritional requirements of the growing embryo may be met by the passage of metabolites from the trophoblast into the vessels within the villous stroma. Vascularization does not extend outwards to the limits of mesodermal invagination into the trophoblast, and so the developing villous tree is divided into two parts, a peripheral zone of primary avascular villi and a more central zone of vascularized villi, intimately related to the intervillous maternal blood spaces. The zone of primary villi is concerned solely with the anchorage of the conceptus to the maternal decidua; with the general growth of the foetus and its surrounding structures, this line of anchorage assumes an irregular line with invaginations deep into the substance of the placenta. This union between trophoblastic shell and decidua is characterized by a zone of acidophil fibrinous material resulting from the serous oozing from eroded maternal blood spaces and by cytolytic degeneration of surrounding decidual cells (Wislocki and Bennett, 1943). It persists through pregnancy and appears at term as irregular hyaline bands stretching from the decidua basalis deep into the substance of the placenta. Within the placental substance, fibrin deposition may occur from several causes, but the fibrin material associated with the embedding process may be recognized and distinguished from pathological fibrin deposition, by the identification of the avascular primary villi within its substance (Fig. 1).

HORMONE PRODUCTION BY THE PLACENTA

In early pregnancy there is histological evidence of extremely active growth and functional activity of both elements constituting the trophoblast. The active mitoses to be seen in the cytotrophoblast as compared with occasional amitotic divisions in the syncytiotrophoblast suggest that during the active development of the villous trees, syncytiotrophoblast is continuously being generated from the underlying cytotrophoblast. At this stage both layers are rich in ribonucleoproteins, which gradually diminish as pregnancy advances (Dempsey and Singer, 1946; Dempsey, Bunting, Singer and Wislocki, 1947; Wislocki, Dempsey and Fawcett, 1948). These authors have associated the presence of ribonucleoprotein with active protein synthesis within the trophoblast, and in particular with the elaboration of plasma proteins before the foetal liver becomes functional, and with chorionic gonadotrophin production during pregnancy generally. Tenny and Parker (1939) hold the view that actively proliferating cytotrophoblast is the source of chorionic gonadotrophin, and Wislocki and Bennett (1943) also showed that the curve of gonadotrophin excretion parallels the rise and decline of the cytotrophoblast rather than the slowly increasing syncytium. A persistence of gonadotrophin excretion however, after its peak production at about 10-weeks gestation, over a period when cytotrophoblast is minimal, suggests that chorionic gonadotrophin production is a function not only of cytotrophoblast but also of its daughter syncytiotrophoblast.

The evidence regarding the site of steroid hormone production in the placenta is less conflicting. Droplets stainable by the usual fat stains, the Sudan range and osmic acid, are found almost exclusively in the syncytium (Fig. 2). Wislocki *et al.* (1948) demonstrated that these fat-staining droplets contain substances with ketone groupings, that like all unsaturated steroids they exhibit autofluorescence to ultra-violet light, and that they are anisotrophic, a characteristic of steroids with ionized terminal radicles. It might be expected therefore that any condition resulting in syncytial degeneration would be accompanied by evidence of decreasing steroid production. In the earlier section of this paper the relationship between declining levels of pregnanediol excretion and pregnancy toxaemia has been demonstrated. It will be shown later that in cases of pregnancy toxaemia where syncytial degeneration is present there is a diminution in lipoid content of the syncytium.

Vascular and Stromal Changes in Normal and Abnormal Pregnancy

Approaching the study of placental insufficiency from a consideration of its vascular supply, Walker and Turnbull (1953) and Mackay (1957) showed that the levels of oxygen saturation in both arterial and venous blood in the foetus are significantly lower in pre-eclamptic toxaemia than in normal pregnancy. Similar conclusions were reached by Browne and Veall (1953) who, studying the dispersion of radioactive sodium, calculated that the flow of blood through the placenta was diminished in pre-eclamptic toxaemia and in essential hypertension to approximately one-third of normal. Because of the systemic vascular involvement in essential hypertension, they suggested that the cause of the ischaemia was primarily extra-placental, but the effect might be augmented by pressor substances resulting from the reduced flow through the placenta.

Records of observations on the histology of the placenta in the later stages of gestation, particularly in respect of toxaemia and essential hypertension, are few. Many of the difficulties in this regard have stemmed from the fact that, with changing function, the placenta undergoes changes in histological pattern, changes which have been termed aging of the placenta; in the interpretation of the histology of the placenta regard therefore must be paid to the normal aging changes for the particular duration of gestation. In the early life of the placenta, the villous stroma consists of a mesodermal core closely resembling Wharton's jelly and hence capable of ready adaptation to the growth and arborescence of the overlying trophoblast. As development proceeds, there are laid down in the stroma collagen fibres which gradually become coarser and thicker; the blood vessels in the villi change from primitive vascular tubes to vessels with a minimal muscular coat enclosing adult type endothelium; the vessels of the villous stalks develop well defined muscular coats in order to deal with the increasing volume of circulating blood demanded by the growing foetus. The trophoblast gradually becomes reduced to a two layered syncytium by about the 32nd week of gestation. Thereafter the appearance of the syncytium is modified; the villous capillaries, hitherto situated well within the villous stroma migrate outwards towards the periphery to form placental sinusoids probably in response to the increasing gaseous exchange requirements of the foetus, and over these sinusoids a very thin layer of syncytium is stretched, the remaining syncytium being piled up at the sides to form syncytial knots.

In pregnancy toxaemia, degenerative changes in the spiral arterioles of the decidua have been noted in a proportion of cases by Sexton, Hertig, Read, Kellogg and Patterson (1950), but because, in the normal process of placental separation, the decidua is destroyed, direct observations on these vessels are usually impossible. Zeek and Assali (1950) have suggested that any vascular changes in the basal decidua would be paralleled by similar changes in the parietalis and have demonstrated that the decidual vessels at this site show, in a high proportion of toxaemic cases, what they describe as "acute atherosis".

Histological Patterns in Essential Hypertension and Pre-eclamptic Toxaemia

During the past two years some 563 placentae have been examined histologically by one of us

(C.G.P.) in this hospital. These have derived from normal pregnancies, from pregnancies associated with essential hypertension and with pregnancy toxaemia, and from a heterogenous collection of conditions including diabetes, erythroblastosis, accidental haemorrhage and sundry other conditions. These placentae were examined with two main objects in view; particular attention was paid to the presence of atrophic changes in the trophoblast, and to vascular abnormalities in the decidua, villous stalks and the villi themselves to see if there were any significant departures from the normal pattern for the individual durations of pregnancy: an attempt was made to correlate any such changes with the levels of pregnanediol excretion. No absolute relationship was found between the clinical diagnosis and the histological pattern, nor between the latter and the level of pregnanediol excretion; this was not surprising in view of the great variation in severity of the different clinical conditions. On the other hand, in the more severe cases of essential hypertension and pregnancy toxaemia, there emerged a fairly clear pattern described below.

Essential Hypertension

In the decidua, thickening of the medial coats of the spiral arterioles, with proliferation of the intima was occasionally seen, but opportunities for observing such arterioles in normally delivered placentae were rare. Thromboses in the decidual veins were more common (Fig. 3) and these were associated either with local and recent decidual haemorrhages, or with a reticular fibrin deposition replacing considerable areas of the placental bed (Fig. 4). The extent of such haemorrhages varied considerably. At their maximum they caused sufficient retroplacental clot as to be responsible for accidental haemorrhage. Frequently the neighbouring intervillous blood spaces were affected and intervillous fibrin deposition was demonstrable (Fig. 5). Interference with the nutrition of the local trophoblast under such circumstances resulted in so-called "infarct" formation, but in such affected areas a residual foetal circulation through the villous cores could be seen (Fig. 5). These decidual changes were also found in some cases of accidental haemorrhage but were not seen in normal full-term deliveries.

On the foetal side, the changes seen were compatible with premature ageing, particularly of the vessels of the villous stalks and the stroma of the villi themselves. The vessels showed medial thickening and endarterial proliferation, often amounting to obliteration (Figs. 6 and 7). The stroma of the villi showed a deposition of coarse adult type collagen at a prematurely early stage of gestation, so that the villous blood vessels tended to be set within the villous stroma, and their outward migration to form sinusoids was minimized or prevented (Figs. 8 and 9). The trophoblast usually showed no greater degree of degeneration than that of placentae from normal cases of similar duration of gestation.

Pre-eclamptic Toxaemia

Wislocki and Dempsey (1946), in a comparison between normal placentae at term and the placentae from cases of eclampsia, drew attention to certain degenerative changes in the syncytiotrophoblast in eclamptic cases. The changes, which affected only a proportion of the villi, were extreme thinning of the trophoblast, a loss of cytoplasmic basophilia and affinity of the nuclei for basic dyes, and an increase in phosphatases in the syncytium.

A series of 161 cases of pregnancy toxaemia studied here showed a general agreement with their findings. The syncytium was grossly thinned over a large proportion of villi, and in addition a diminution was demonstrable in the amount of lipoid material stainable by osmic acid, in the syncytium (Figs. 10 and 11). In places the thinning of the syncytium was so marked as to give the appearance of loss of continuity over the villous stroma, and the villi thus affected showed variable amounts of acidophil hyaline material within the stroma. This was interpreted as a slow deposition of fibrin from the maternal intervillous blood spaces following the loss of the syncytium which forms part of the lining of such blood spaces. Where this change affected adjacent villi fusion was of common occurrence (Fig. 12).

In a proportion of cases of pregnancy toxaemia vascular changes and their sequelae,

FIG. 1

Avascular primary anchoring villi embedded in fibrin within decidua; from a normal full-term pregnancy. ×145.

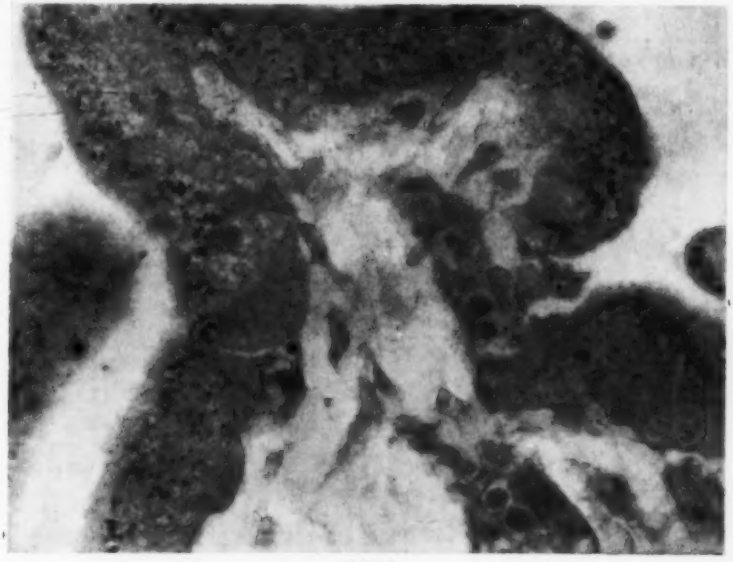

FIG. 2

Villus from ectopic tubal pregnancy (7 weeks), stained by osmic acid to show lipoid distribution in syncytiotrophoblast. ×525.

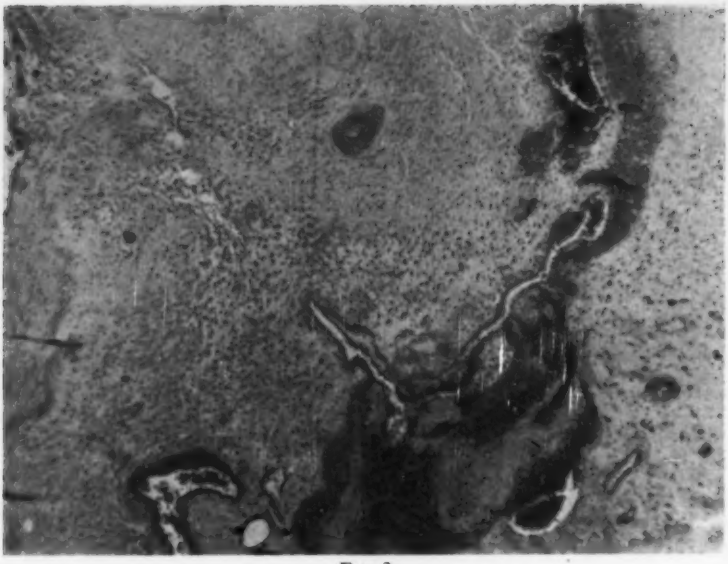

FIG. 3

Recent and old venous thromboses with decidual necrosis; from a case of essential hypertension, delivered at 37 weeks. ×45.

FIG. 4

Reticular fibrin deposition following decidual haemorrhage; from a case of essential hypertension delivered at 40 weeks. ×145.

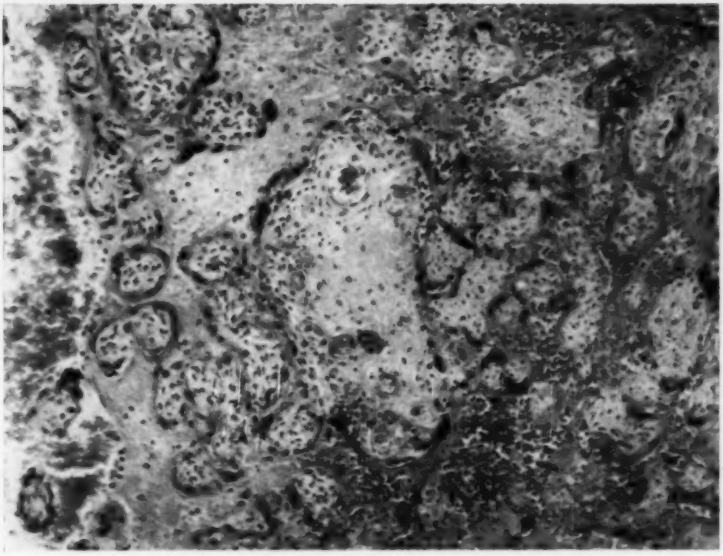

FIG. 5

Intervillous fibrin deposition and early "infarct" formation, with persistence of foetal circulation; from a case of essential hypertension delivered at 30 weeks. ×145.

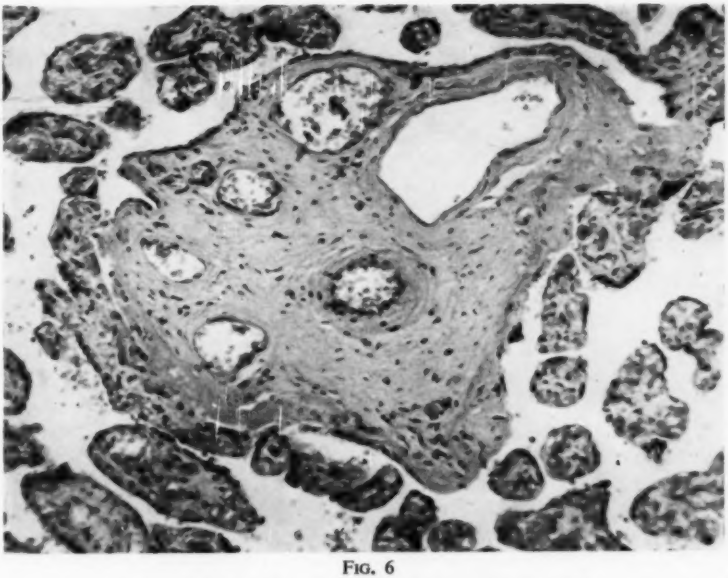

FIG. 6

Villous stalk from a normal full-term pregnancy. ×145.

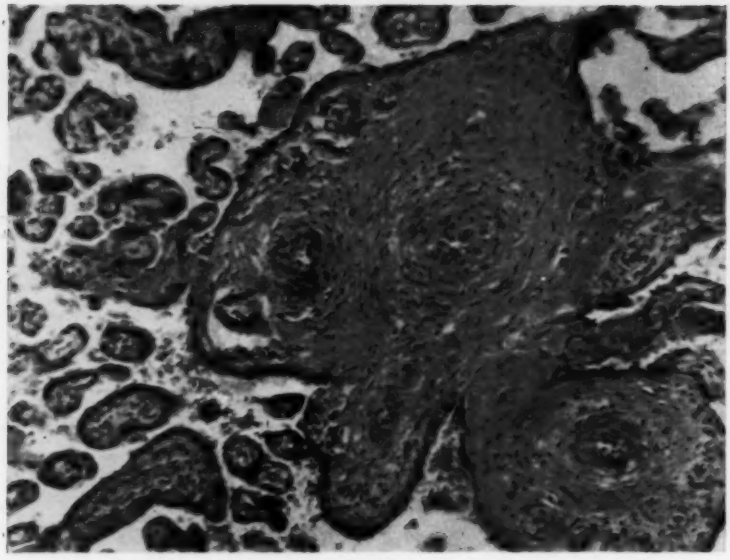

FIG. 7

Villous stalk showing vascular thickening and obliterative change, with stromal fibrosis; from a case of essential hypertension, delivered at 39 weeks. ×145.

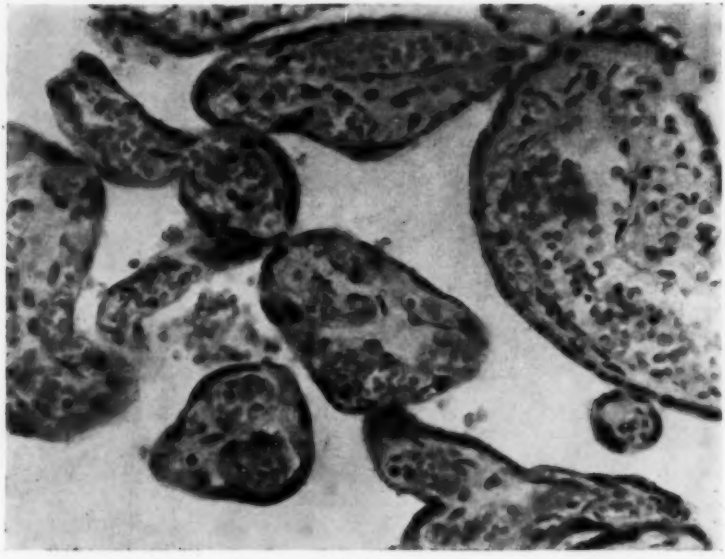

FIG. 8

Sub-trophoblastic sinusoid formation in a normal full-term placenta. ×300.

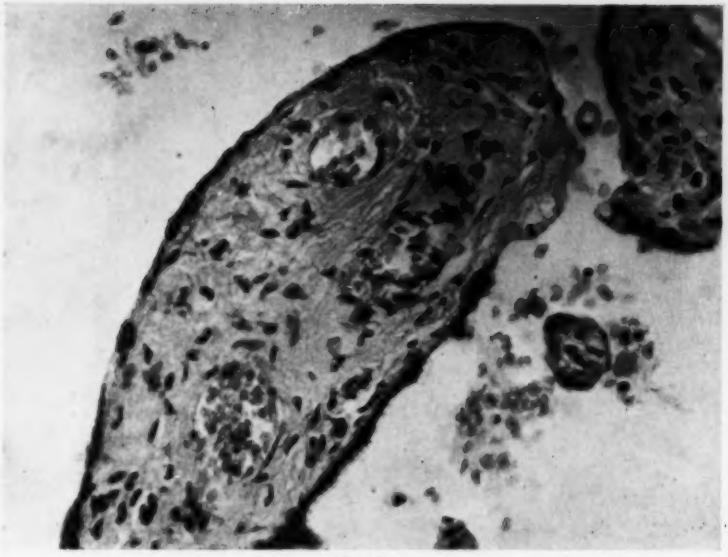

FIG. 9

Premature fibrosis in villus, with prevention of sinusoid formation; from a case of essential hypertension, delivered at 40 weeks. ×300.

FIG. 10

Normal full-term placenta, showing trophoblast survival and lipoid droplets in syncytium (osmic acid). ×300.

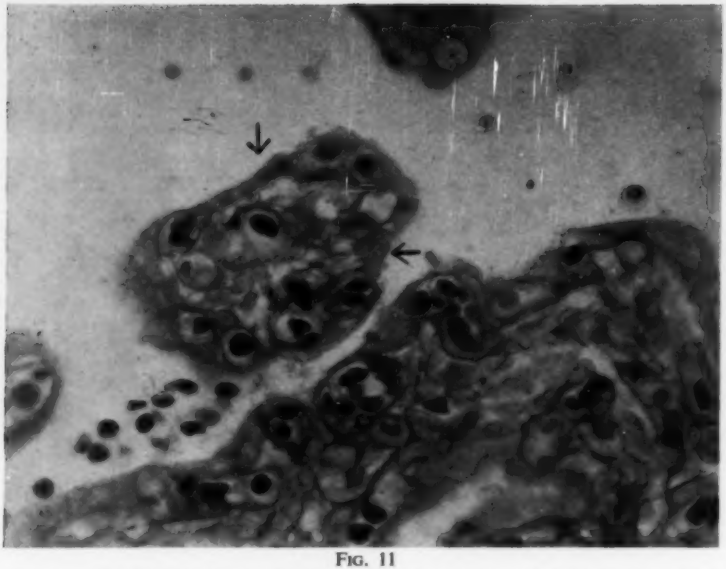

FIG. 11

Villi showing trophoblastic atrophy and relative disappearance of lipoid droplets (osmic acid), from a case of pregnancy toxaemia delivered at 35 weeks. Pregnanediol excretion range during last four weeks, 17·2 to 10·0 mg. per diem. ×300.

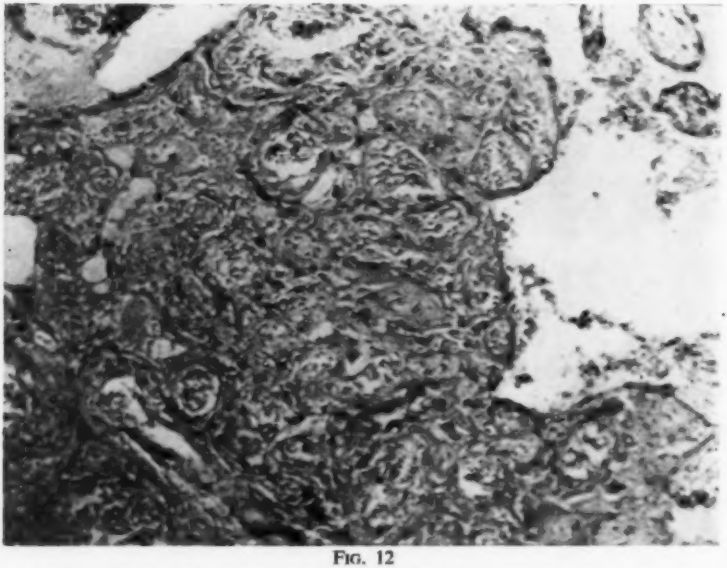

FIG. 12

Intravillous fibrin deposition with fusion of villi, following trophoblastic atrophy; from a case of pregnancy toxaemia, delivered at 34 weeks. ×145.

identical to those seen in hypertension, were also apparent. Such changes were absent from those cases of "acute" toxaemia manifesting itself for the first time in the last few weeks of pregnancy and in which delivery either normally by induction or Caesarean section followed soon after the disease process manifested itself clinically; but in cases where pregnancy toxaemia persisted over several weeks both vascular and syncytial changes were apparent.

Review of Material

In the series of placentae examined, besides those from cases of essential hypertension and toxaemia, there were a number from cases of erythroblastosis and diabetes. The histological appearance of these latter did not differ essentially from the well-known pattern in these conditions.

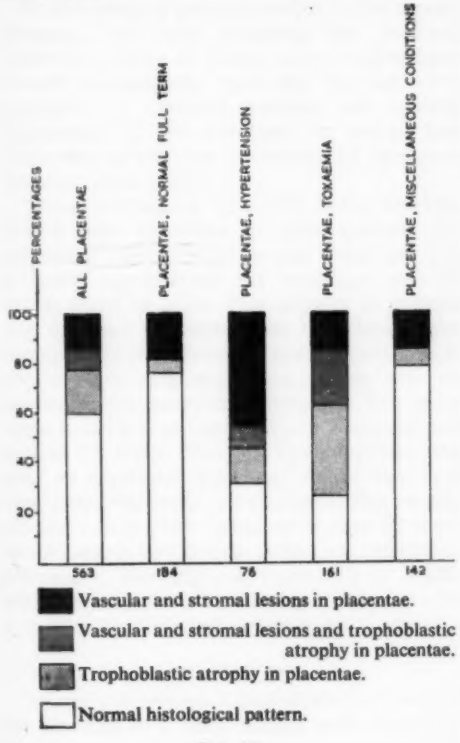

FIG. 13

In this review, emphasis was placed upon the presence of syncytial atrophy, and upon vascular and stromal changes within the villi; an attempt to summarize the whole picture is shown in Figure 13 which represents an analysis of the frequency of occurrence of these two aspects of placental histology under the various clinical headings. It will be seen that whereas both syncytial atrophy and vascular and stromal changes are to be found in a proportion of all placentae, there is a marked preponderance of vascular and stromal change findings in cases of hypertension and a corresponding increase in frequency of syncytial atrophy in cases of pregnancy toxaemia.

CONCLUSIONS

The main features of aging in normal placenta tissue are a slow but progressive thinning of the syncytium, a gradual thickening of the blood vessels of the villous stalks and villi, and a progressive conversion of the foetal type mesoderm of the villous stroma into adult type fibrous tissue. Both the vascular and stromal changes and the syncytial atrophy are accelerated in essential hypertension and in pregnancy toxaemia, the emphasis in the former condition being seen in the vessels and stroma, and with the latter in the syncytial atrophy. The effect of this acceleration of the aging process in hypertension appears to be directed towards a reduction in the area of functional placental bed, and, by the limitation of villous sinusoid formation, to an interference with simple metabolic and gaseous exchange in the later weeks of gestation. In pregnancy toxaemia, premature syncytial atrophy is accompanied by a reduction in syncytial lipoid, and this relates to the generally lowered values for pregnanediol excretion in this condition.

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FASCIAL SLINGS FOR STRESS INCONTINENCE

BY

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IN his famous work on the art of obstetrics William Smellie (1876) refers to what was probably as common a complication of childbirth in the 18th century as now, namely, the involuntary passing of urine or stress incontinence. Writing as an obstetrician he made the pawky observation "the cough may be alleviated by the proper remedies!"

In the group of patients studied in this report, however, not only coughing but walking, descending stairs or lifting quite small weights caused incontinence; moreover, the distressing symptom of constant wetness was usually aggravated by the fact that the patient had subjected herself once or oftener to operation without improvement.

We have observed the results of the Aldridge fascial sling operation in some patients for periods of up to 7 years so that it was felt that a useful appraisal of the technique and its results could be made. The majority of patients had had one or more pelvic floor repairs for prolapse and stress incontinence. The anatomical results were satisfactory, i.e., there was no apparent cystocoele and rectocoele but gross stress incontinence remained as a persistent and serious disability. The sling operation was also used as a primary procedure in the very rare case where the writer felt that pelvic floor repair offered a very poor chance of a cure of stress incontinence, for example, when a short vagina followed a Wertheim's hysterectomy or irradiation therapy, or in the elderly multipara with a narrow introitus and no prolapse.

CASE SELECTION

All our patients have been studied in hospital for upwards of a week mainly with the object of eliminating all other conditions except simple stress incontinence. Routine physical examination, urine analysis, cystoscopy, intravenous pyelograms and cysto-urethrograms were carried out. Preliminary cysto-urethrograms were taken mainly as a matter of interest to show the posterior urethro-vesical angle. Although our experience is limited we have not found the test of practical value in the pre-operative assessment of cases and we have noted with other workers that stress incontinence may co-exist with a well-marked angle on straining when we expected to find a poor one.

Our ward sister's reports on the patients' habits and demeanour are also carefully noted; a special note is made of frequency of micturition or nocturia. Senile bed-wetting has excluded a few of our older patients. Urge incontinence without clinical evidence of disease in the renal tract was common but if rest in hospital cured the condition to the extent of permitting an undisturbed night's sleep then a sling operation was undertaken to cure the residual stress incontinence. Careful examination of the nervous system and, on occasion, help from our colleagues in psychiatry has been necessary in borderline cases; but there were also patients whom we ourselves labelled as being "odd" and not suitable for a sling operation. For example, we have watched several patients, alleged to have gross stress incontinence, carry out vigorous exercises with full bladders without any leakage of urine, while we singled out two patients who coughed violently at examination without incontinence and then after a definite pause proceeded to micturate in a powerful and steady stream to the peril of the examiner! Lastly, pelvic floor exercises have been tried as a preliminary to operation in most of our cases without a single success. We have no experience

of the Kegel (1948) perineometer which is used to record the gradual recovery of power in the muscles of the pelvic floor.

Borderline Decisions

I have twice set out with some misgivings to undertake a plastic repair in the absence of more than a slight cystocoele for the tissues were poorly developed and scarcely able to hold even a fine suture; I abandoned the attempt, proceeding to the insertion of slings with complete success. This approach to the difficult problem of selecting the correct operative technique for the individual case must not be confused with a combined plastic repair with the insertion of slings which in Germany is referred to as the insertion of a "safety band" (Schützverband) (Martius, 1947).

Presented with a case of stress incontinence it is our practice to repair any prolapse with special attention to buttressing the urethra; if stress incontinence persists then slings are inserted at a second operation so that our results represent the curative effect of slings after a plastic repair has failed.

In the past 3 years I have tried to single out the difficult or "problem" patient where a case could be made for attempting a cure of stress incontinence by a second plastic repair or even a third plastic repair if there was a slight but definite recurrence of cysto-urethrocoele. Operating with my colleague M. J. D. Noble an attempt has been made to advance the bladder on the cervical stump prior to completion of a high anterior colporrhaphy with the maximum of kinking or bowing of the urethra. It has been useful in this problematical type of case to explain to the patient that no absolute guarantee of a cure of stress incontinence can be given so that a failure or partial success is accepted and no objection offered to what she has been told may be necessary, viz., the second part of the operation, the insertion of slings.

Why the Aldridge Operation?

Dr. A. H. Aldridge (1956) sums up his views:

"All previous techniques except that of Price had made a point of transplanting muscles or fragments of muscle alone or with fascia with the hope that muscular contractility would be retained. From a study of these techniques it seemed obvious to me that none of these muscles could be transplanted to the positions recommended without almost complete destruction of their nerve and blood supply. For this reason I did not see how they could be expected to retain their function as muscles.

"The thoughts I had in mind in devising the technique were:

"(1) Choice of a muscle which was always well developed and could be utilized without transplanting which was sure to damage its nerve and blood supply. The recti muscles seemed the logical ones and the only ones which could be used in this way.

"(2) Use of fascial strips which could be to some extent left attached with the hope that their vitality would be retained. Detached fascial strips as recommended by Price had been found unreliable for repair of hernias.

"(3) Fixation of the sling at a point well above the pubic crest to provide an upward and forward pull on the urethro-vesical angle during strain when the recti muscles contracted (Aldridge, 1942). For slings by previous techniques, muscle and fascial structures had been passed backwards directly above or below the pubic bone which allowed no changes in position during strain and contraction of the abdominal muscles.

"I believe adherence to the three points outlined above led to success where the previous techniques had failed. Jeffcoate's (1952) and Roberts' (1953) observations seem to offer the best explanation for the success of the sling.

"There can be no doubt that the Germans had priority on the idea of creating a supporting sling for the urethra by utilizing the structures from the abdominal wall, or that they should be given full credit for their efforts. I assure you that my feelings will not be injured if you describe my technique as a modification of the Goebell-Frangenheim-Stoeckel-Price technique, or any combination of the above which you choose."

At operation and at follow-up examination we have often discussed the mechanism whereby slings achieve a cure of stress incontinence in the individual case. At operation the urethra is certainly compressed by slings so that the catheter is gripped from below and on the sides but this closure of the upper urethra does not prevent the passage of a large bougie. Secondly, the urethra is freed of all scar tissue at operation so that the slings cause a marked kink. To micturate, this obstructive kink has to be passed and, as will be shown later, several of our patients have to adopt half-standing positions to relax their fascial slings to complete the act of micturition. How this position of semi-flexion relieves kinking is not clear. On the one hand, at operation we have palpated the slings

per vaginam asking the anaesthetist to make the patient cough as she recovered from the anaesthetic but there is practically no "tugging" effect as the abdominal muscles contract. On the other hand, at follow-up examination there appears to be a definite tugging or increase in the kinking of the urethra when the patient voluntarily coughs so that Aldridge is probably right in his explanation of the *modus operandi* (Para. 3 above).

How long the slings survive is doubtful. One of our patients noticed a return of stress incontinence immediately after falling off a 'bus (when possibly the fascia broke) but we have, nevertheless, observed what appeared to be normal (white) healthy fascia months after operation in several patients who required removal of nylon or silk sutures. The life of the fascial slings is often, however, a matter of conjecture in the successful case but it is of interest that in our two repeat operations we saw no sign of the previous slings.

Lastly, we have observed in a virginal case for whom we undertook a primary sling operation that slings not only kinked the upper urethra but cured a considerable degree of vault and uterine prolapse which before operation had allowed one to pull down the cervix at least 2 inches. There was no cystocoele or rectocoele and the vagina barely admitted one finger. Whether the kinking or freeing of the urethra or fixing of the bladder base (and the uterus) was the main factor in effecting a cure is not certain but she has remained continent for 6 years.

From the literature (Read, 1950; Millin, 1950; Ardran *et al.*, 1956) and from our own observations, it is clear that there are many factors which may produce stress incontinence so that it is not surprising that in the individual case it is not always possible to be certain as to how slings produce a cure. But the main principles as outlined by Aldridge explain most cures, viz., freeing of the urethra to allow a kink by the slings which is probably increased by the pull of the abdominal muscles, e.g., in the act of coughing.

Operative Technique

Our technique largely follows Aldridge (1942). A 12-inch to 15-inch transverse skin incision above the symphysis exposes the fascia of the external oblique muscle. The fascial flaps are planned to have their firm medial attachments centrally just above the symphysis pubis. An excess of fascia can be cut off but a short flap may not permit the operation to be completed, so that they are made as long as possible. Six to 7 inches (15 to 17·5 cm.) is the average length of each sling, ¾ of an inch (2 cm.) the breadth, and if the medial end is sited close to the midline no devious route for the flaps will take away from its length as it passes down to the vagina. The site of the upper end of the fascial tunnels is selected and opened in its upper part by finger and scissors dissection behind the symphysis pubis towards the lateral urethra as it emerges below the subpubic angle. A strong nylon suture is attached to the end of the flaps with knots in its length so that it may be grasped later by long (Bozeman's) packing forceps passed up from the vagina. The gap made by the fascial slings in the external oblique fascia is sutured as far medially as tension permits.

Vaginal Exposure

I have only once had to use an episiotomy to obtain exposure of the anterior vaginal wall but there is no reason why one should not be used to get a good exposure of the anterior vaginal wall. Twenty to 30 ml. of Procaine (½ per cent) with 0·5 ml. of 0·1 per cent adrenaline is injected deep to the mucosa of the anterior vaginal wall which is then incised in the midline and freed laterally.

The whole urethra is exposed up to its vesical junction and beyond with wide freeing of scar tissue as far laterally as possible. The bladder base and the urethro-vesical junction and surrounding bladder are now quite free from attachment to scar or periosteum, and the internal urethral orifice can be located by palpating the tip of a self-retaining catheter. It is important that this freeing is complete for it allows the bladder neck to be elevated high behind the symphysis pubis by the slings.

If there should be a small bulge of bladder superior to the internal urethral meatus it is repaired with a purse-string suture of fine catgut. By a combination of cautious snipping with long scissors and boring with the finger, tunnels for

the slings are now made beside the urethra upwards and behind the symphysis pubis. A 12-inch closed Bozeman's packing forceps is guided close to the pubic periosteum but clear of the bladder while the guiding finger presses against the urethra outlined by the catheter. The cave of Retzius is traversed until a slight push passes the point of the closed forceps to one's assistant at the selected site near to the attached base of the slings. On only one occasion have I met real difficulty in passing down slings, due to the fact that the flaps had been inadequately cleared of fat; as they were pulled down fat and fascia "mushroomed" off to make a plug and block further descent. The cause was recognized and cleaning of the flaps allowed of their descent and successful completion of the operation. The upper tunnel made from the abdominal incision is also important in allowing the slings to pass down without difficulty and one's assistant's finger passed down serves as a guide to the ascending forceps.

Tension in the Slings

The fascial flaps are crossed beneath the urethra and sewn with fine nylon thread cut short on a treble tied knot. Further sutures (usually 3 or 4) are inserted until the urethra ascends with the widely mobilized urethrovesical junction behind the symphysis pubis. Any redundant fascia is cut away with the guide sutures. I have found it difficult to assess the degree of kinking necessary to cure stress incontinence without incurring the risk of post-operative retention. Lowering of the legs from lithotomy before tying the final suture, or pulling on the catheter to ascertain when it is gripped by the slings, in our experience offers little guidance as to the exact tension for the individual case. In our two worst cases of post-operative retention a large cystoscope could be passed with ease and the kinking of the urethra produced by the operation was not exceptional. It seemed that our operation had not only provided a mechanical barrier to micturition but had also upset the normal neuromuscular co-ordination so that the more the patient strained the more she failed to relax the urethral sphincter or overcome the kink or barrier at the upper vagina.

Vaginal Closure

In our experience there is little vascular oozing at operation after the slings are tied, but we do not follow the Aldridge technique in that we leave the vaginal mucosal incision open although the edges fall together so that any delayed oozing of blood may escape into the vagina. As in all my plastic repair operations no vaginal pack is used but a self-retaining catheter is inserted for 5 days. The operation disturbs the patient little and ambulation after 24 hours is the rule.

Clinical Material

Twenty-one of the 28 patients had been operated on for stress incontinence by the technique of pelvic floor repair on one or more occasions so that any degree of prolapse whether cystocoele, rectocoele or descent of the vault had already been dealt with. Eight patients without prolapse were operated on by a primary sling operation.

Results

Duration of follow-up:

Up to 6 months	3
Up to 9 months	2
Up to 18 months	5
Up to 2 years	2
Up to 3 years	2
Up to 4 years	4
Up to 5 years	3
Up to 6 years	5
Up to 7 years	2
Total	28

Total number of operations	28
Repeat sling operations	2

Of 28 initial Aldridge operations:

Cured	22	
Improved	4	
Unimproved	1	Failures
Relapse after 1 year	1	Failures
Relapse after 2 years	1	
Relapse after 4 years	1	

Case 1: Failure

Mrs. F., aged 70, was a rather frail woman who 12 years ago had a radical vulvectomy with lymph node dissection for carcinoma of the

vulva by the late Sir Beckwith Whitehouse. Increasing stress incontinence over the past few years had led to severe vulvitis.

The vagina was narrow but one finger could be passed without difficulty. There was no prolapse but gross stress incontinence was obvious. Exercises aimed at improving control of micturition were not effective. Although it is my practice to attempt to cure stress incontinence by a plastic repair with special attention to urethral buttressing, after much thought in this case I concluded that the chance of a cure in my hands was low. An Aldridge operation was therefore carried out as a primary procedure. Her stress incontinence, however, was unimproved.

Case 2: Moderate Improvement

Mrs. B., aged 50. A colleague had attempted to alleviate her residual stress incontinence by an intravesical operation aimed at narrowing the internal sphincter urethra; the result was disastrous. On the gentlest movement in bed, urine was passed involuntarily. There was no prolapse and at examination a large self-retaining catheter actually fell out with its own weight while upthrust of fingers in the region of the urethro-vesical junction caused a flow of urine. We agreed, however, that at least we could not make her worse and we might make life more bearable if firm slings were made to pull up a large kink in the urethra.

As a result of her primary Aldridge operation she is continent when upright so that she can go about her ordinary work at home without protective clothing. A cough of unusual violence leads to slight incontinence, while stooping causes considerable leakage. The patient, however, considers that she is almost cured, i.e., she can lead a normal life at home and is able to shop, visit friends, etc. From being a depressed and miserable woman she has become cheerful and full of vigour.

Complications Following the Aldridge Operation

(a) *Post-operative Retention*

The resumption of normal micturition after a sling operation is not always easy in our experience, and this difficulty tends to be much more prolonged than after any form of pelvic floor repair. To resume normal micturition without partial retention or even occasional complete retention took

21 days in 7 cases
30 days in 3 cases
38 and 46 days in 2 cases

We have found it of value to explain to the patient that at the start the normal flexed position at micturition may have to be altered to the half-standing position for at least the first few days. Whenever difficulty with micturition becomes apparent a large dilator is passed *per urethram*; this is reassuring to the patient and is often followed by much improvement.

In one of our cases we think some form of neurosis played a part but the sling operation undertaken was not an Aldridge type of operation, viz.:

Case 3. Mrs. X., aged 50. In 1949 an Aldridge operation brought improvement in her stress incontinence, but within a year she relapsed. We hesitated to attempt a further repair using slings and considered that a further plastic repair would not be successful. Four years later she was most anxious to have relief from her stress incontinence. First of all, strict dieting reduced her weight from 180 pounds to 140 pounds. Following preparatory pelvic and abdominal muscle exercises a hammock-shaped flap of fascia lata 8 inches $\times 1\frac{1}{2}$ inches was detached and inserted vaginally. The ends were pulled up into the abdomen and sutured to the rectus sheath. The mobilized urethra and base of bladder were raised high behind the symphysis pubis and a considerable kinking of the urethra resulted.

Partial and on occasions complete retention lasted for 90 days although a large cystoscope could be passed with ease. The patient naturally became very anxious and thought finally that she would never pass urine normally. She was cured, however, by the daily passage of large bougies and her stress incontinence has remained cured for over 3 years. The operation was not of course an Aldridge sling and the urethral kinking was exceptional.

(b) *Return of Urgency and Occasional Urge-incontinence*

We have pointed out that as a pre-requisite to operation absence of urgency and urge incontinence was confirmed by observation, first in outpatients and finally with periods of up to 2 weeks of rest and observation in hospital. In 13 patients (46 per cent), however, symptoms of urgency and occasional urge-incontinence were present and apparently cured prior to operation only to return after a variable interval. This recurrence of urge-incontinence however is only serious in 5 and no worse than before operation. The patients have become accustomed to the condition having learned not to delay unduly the emptying of their bladder. Investigation of the urinary tract has proved entirely negative. In summary, then, after an Aldridge sling operation symptoms reappeared as follows:

Urge incontinence a definite disability	5	
Mild urge incontinence ..	8	
Total	13	(46 per cent)

(c) *Difficulty in Emptying Bladder*

Eleven of our patients must on occasions adopt a half-standing position to empty the bladder although none consider this a serious drawback to the operation. We presume that the half-standing position relieves the fascial tension to reduce the kinking effect of the sling on the urethra. It is puzzling that some patients with difficulty in emptying their bladder have months of freedom from difficulty.

(d) *Haemorrhage, Sepsis, Fistula*

We have encountered no serious bleeding, sepsis or fistula. When silkworm gut was used to join the slings in the vagina we had occasionally to remove the bristling sutures from the vagina after periods of up to 6 months. With short sutures of fine, strong nylon thread this complication has been met only once in the last dozen cases. There have been no cases of post-operative hernia.

(e) *Post-operative Calculus in Successful Operations*

Case 4. Mrs. C., aged 58, was referred by a colleague who had carried out a pelvic floor repair to produce a perfect "anatomical" result which however did not cure her stress incontinence. Following an otherwise successful Aldridge sling operation she had occasional partial retention of urine and after leaving hospital she complained of bladder pain especially on walking with a return of partial retention of urine. Ten weeks later on re-admission we were surprised to find a large vesical calculus which, of course, was absent at routine cystoscopy and X-ray prior to operation. The calculus was treated successfully by lithotrity by my colleague in the Department of Genito-urinary Surgery, Mr. Hugh Donovan.

A second example of post-operative calculus not included in our series followed a sling type of operation where ox fascia was used to replace the abdominal fascia of the Aldridge operation. My colleague, Mr. A. L. Deacon, carried out the operation at a clinical demonstration. Once again it was over 4 months before we realized that the patient had something more than cystitis and an anxiety state. A large bladder calculus was obvious at cystoscopy and once again it was successfully treated by Mr. Hugh Donovan by lithotrity with complete relief of symptoms including stress incontinence. Although we are not certain of the origin of these stones the second one was thought to consist of phosphatic deposits perhaps on a nucleus of oil which was the basis of the radio opaque substance then used at cysto-urethrogram.

C. Scott Russell (1956) has suggested that phosphatic calculi, or at least deposits, can be prevented by keeping urine acid with ammonium chloride and in a personal communication he recommended polythene catheters in place of our present rubber catheters.

Relapse After Slings

Three cases relapsed, after 4 years, 2 years and 1 year respectively, the last being classified as a failure. Case 1 was cured by a repeat Aldridge operation, Case 2 by repair of a recurrent prolapse which had appeared and gradually increased after the sling operation. Case 3 was

cured by a type of sling operation using a wide detached band of fascia lata with its end sutured to the fascia of the external oblique muscle; details of the persistent retention of urine after this operation are given above.

Primary Use of Slings

In the past 3 years I have usually considered it wise to repeat a plastic operation even if it might not be expected to cure stress incontinence, e.g., in a recurrent case of stress incontinence following an apparently perfect plastic repair, or in a nullipara with a stenosed menopausal vagina. In the earlier years of assessing the Aldridge sling operation, however, I carried out 6 primary operations without a preliminary attempt at pelvic floor repair, and 18 months ago a further 2. A total of 10 is reached if 2 further operations are included on patients who had had plastic repairs over 10 years previously. In each case I felt almost certain that in my hands a pelvic floor repair would fail to cure stress incontinence and the sling operation was selected, viz.:

1. Mrs. Br., para-3, age 53. Obese. Stenosed upper vagina.
Result: a cure—8 years.

2. Mrs. Ba., nullipara, age 40. Very obese. No prolapse.
Result: a cure—6 years.

3. Miss B., nullipara, age 63. Thin. One finger possible *per vaginam*. No cystocoele or rectocoele but the uterus which was atrophic prolapsed 2 inches on straining.
Result: a cure—7 years.

4. Mrs. C., para-3, age 48. Radium menopause, 1944. Marked introital stenosis. No prolapse.
Result: a cure—7 years.

5. Mrs. M., para-3, age 51. X-ray menopause, 1949. Bronchitis and obese. Urethra 1 inch long; small "bulge" of bladder above internal meatus, closed at operation.
Result: a cure—5 years.

6. Mrs. B., para-2, age 50. Previous intravesical repair performed elsewhere actually made her more incontinent. The internal urethral meatus was so lax that a large mushroom-shaped catheter fell out of the bladder under its own weight.
Result: partial cure; able to live a normal life although incontinent on bending. (Referred to above.)

7. Mrs. F., para-1, age 70. 1942—vulvectomy for carcinoma. Narrow vagina: no prolapse but the bladder bulged very slightly above the internal urethra at operation.
Result: failure.

8. Mrs. J., para-7, age 60. Wertheim's hysterectomy (partial vaginectomy) for carcinoma of cervix. Residual vagina 1½ inches with short urethra. Prospect of a cure of stress incontinence by plastic repair considered to be nil.
Result of slings: cure of stress incontinence.

Discussion

A report by Cruttenden (1949) to the Birmingham and Midland Obstetrical and Gynaecological Society in 1949 showed clearly that in our hospitals many cases of prolapse with stress incontinence were not cured by pelvic floor repair; there was residual stress incontinence in 31 out of 116 pelvic floor repairs (27 per cent). Irvine (1955) recently gave an absolute 5-year cure rate of only 50 per cent. Other results are Stallworthy (1940) (taken from patients attending the Chelsea Hospital for Women), 16 per cent; Woodrow Cox (1955), 9 per cent; Pacey (1955), 15 per cent.

A recent personal review of 50 cases of stress incontinence treated by pelvic floor repair by members of our team in the Professorial Unit, Birmingham, gave the following results: cured 44 (88 per cent); failure or part-failure 6 (12 per cent), although on an average only 2 years had elapsed since operation. (Two of our 6 failures, however, had mainly urge-incontinence.) It seems certain, therefore, that any follow-up of pelvic floor repair operations will reveal that at least 10 per cent of patients continue to have a degree of residual stress incontinence.

It would, of course, be invaluable to have some technique to assess each case pre-operatively to select a pelvic floor repair and carry it out with a cure of stress incontinence on 100 per cent, sifting out the inevitable failures for cure by primary Aldridge slings. Unfortunately there is no such clinical method of pre-operative assessment of stress incontinence, but in general one expects better results from pelvic floor repair in women with good tissues where advancement of the bladder is easy. On the other hand, in older patients with poorer tissues and little cystocoele, bladder advancement may be difficult or impossible and a cure of stress incontinence may or may not follow pelvic floor repair. It is in this second group that one thinks of a primary Aldridge operation but in general the policy we have adopted up to the present is as follows: when we encounter one of our own failures after a pelvic floor repair a

careful study is made in hospital to exclude urge-incontinence, neurosis, senility or organic disease of the nervous system. Finally, a further pelvic floor repair is usually selected and every effort is made to buttress and kink the urethra in the plastic repair of the anterior wall, followed, of course, by amputation of the cervix and posterior repair where this is necessary. But with a cure rate in the region of 80 per cent should we proceed to use the Aldridge operation in the recurrent case of stress incontinence without recurrent prolapse rather than suggest a further plastic repair? The answer at present we suggest is:

(1) A further carefully planned plastic repair will possibly cure her.

(2) If a plastic repair is successful in curing stress incontinence, post-operative retention of urine is a most unlikely sequela.

In other words, although a sling operation almost always cures or improves stress incontinence in a properly selected patient, post-operative retention (common but not prolonged after a plastic repair) may mar an otherwise satisfactory operation. Both Jeffcoate (1956) and Moir (1950) refer to this complication after the Aldridge operation.

At present, then, it must be admitted that with our present experience we are in no position to offer a set of rules to guide one to the operation of choice. But over the last 10 years primary sling operations have seldom been carried out; in fact, on only 8 patients (with a further 2 who had plastic repairs 10 years previously), making a total of 10. Eight out of the 10 were cured and 1 much improved. It is important to emphasize, however, that these were borderline or "debatable" cases and that for stress incontinence with slight or obvious prolapse a thorough pelvic floor repair is normally expected to cure both conditions. Working to this plan, however, we are left with the exceptional case where persistent stress incontinence requires further operative treatment. Added to these failures of the plastic technique is the case which only occasionally presents in gynaecological practice in which the absence of prolapse or the presence of vaginal stenosis may justify a primary Aldridge operation.

In all, we undertake the Aldridge operation in our Unit not oftener than 3 or 4 times each year including cases referred by colleagues in neighbouring hospitals who know we are interested in the problem; so that we are in line with Jeffcoate (1956) who undertook only 44 operations in 11 years in a unit of comparable size to our own.

We agree with Moir that patients who present with stress incontinence after one or more plastic operations are often very unpromising clinical material but it should be stated that, once acquired, the Aldridge technique is not difficult and although not without risk the operation is safe. We therefore seldom reject a straightforward case of stress incontinence although dieting, preliminary pelvic exercises or rest in hospital to alleviate bronchitis may be necessary before surgery. Our results are presented with the Oxford and Liverpool series but it should be noted that 13 of the Liverpool group have only been under observation for a year while 12 of the Oxford patients had previously been cured of vesico-vaginal fistula.

Operative Results
(Percentages in brackets)

	Total Operations	Failed	Considerably Improved	Cured
Liverpool:				
Jeffcoate (1956)	44	3 (7)	3 (7)	38 (86)
Birmingham ..	28	2 (7)	4 (14)	22 (78)
Oxford:				
Moir (1950) ..	26	3 (12)	5 (19)	18 (70)

Conclusions

When a plastic repair has cured prolapse (cystocoele, descent of cervix, rectocoele) but has failed to cure stress incontinence Aldridge slings are safe and effective. The cure rate is high and the relapse rate low. The primary operation has a definite place in the rare case of stress incontinence without prolapse, e.g., where the vagina is shortened or narrowed by previous surgery or irradiation.

Case selection requires a careful study of the patient in hospital to exclude other conditions such as urge-incontinence which, of course, may co-exist with stress incontinence.

Summary

(1) Twenty-nine Aldridge operations and one fascia lata sling operation have been carried out on 28 patients. Twenty-two were cured; there were 2 failures, 1 relapse after 2 years and another after 4 years; 4 were improved.

(2) Primary Aldridge operations were carried out in 10 patients: cured 8, improved 1, failed 1.

(3) Three patients who relapsed were cured by (*a*) a repeat Aldridge operation (after 4 years), (*b*) a plastic repair of a recently developed recurrent cystocoele (after 2 years), and (*c*) the insertion of a wide band of fascia lata to kink the urethra.

(4) There were no accidents or complications apart from one vesical calculus formed soon afterwards.

Acknowledgment

Suitable cases for operation are not easy to find so that I was glad to have the help of colleagues in the Midlands who sought out cases and referred them.

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SICKLE-CELL DISEASE AND PREGNANCY

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SICKLE-CELL trait and disease have been reported most commonly in the negro population of the United States of America. This was probably due to lack of adequate medical study of the question in Tropical Africa, since the American Negro is essentially of Central African origin, and recent studies reveal that sickling is of widespread, though variable distribution in African, as well as in various non-African races. Lehmann and Raper (1949) found 45 per cent of sickling among some African communities in Uganda, and Edington (1953) recorded 18 per cent for the Accra Region of Ghana. Allison (1954) considers that the trait may partially protect the bearer from the malarial parasites. The incidence of sickling in Jamaica is up to 5·7 per cent (Jelliffe, Stuart and Wills, 1954).

Among coloured pregnant women, sickling may be quite common, but the trait is far commoner than the various forms of overt sickle-cell disease. Beacham and Beacham (1950) found the trait in 8·3 per cent of New Orleans negroes, with 6 cases of sickle-cell disease in 10,000 deliveries. Smith and Conley (1953, 1954) found sickling in 8·4 per cent of negro out-patients at Johns Hopkins Hospital, and have encountered various forms of sickle-cell disease in pregnancy. Switzer and Fouché (1948) found the ratio of trait to anaemia of 74 : 1 in American negroes. In Great Britain, the recent influx of Jamaicans has resulted in both sickle trait and various forms of sickle-cell disease being encountered in hospital practice.

HISTORY

A brief historical survey of the recognition and nature of the disease is of interest. In 1910 Herrick described many of the characteristic haematological and clinical findings now referred to as sickle-cell anaemia. Emmel (1917) suggested that the sickle-cell phenomenon might be inherited. It was later realized that sickling occurred in two distinct conditions: (*a*) In a peculiar type of severe anaemia—sickle-cell anaemia, and (*b*) as a symptomless trait—the sickle-cell trait (Cooley and Lee, 1926; Neel, 1949).

Taliafero and Huck (1923) again observed that the sickling phenomenon was inherited and suggested that the mode of inheritance was that of a Mendelian dominant. Neel (1951) has postulated that the sickling phenomenon is due to a gene, which, in single doses produces the heterozygous trait, in double dose the homozygous state with development of sickle-cell anaemia.

In 1949, Pauling, Itano, Singer and Wells demonstrated by electrophoresis that sickling was associated with an abnormal haemoglobin, now called S. In the trait, S occurs together with excess of normal, adult A haemoglobin, whereas in the anaemia all the haemoglobin is S, or some foetal haemoglobin accompanies it (Singer, Chernoff and Singer, 1951). The peculiar physical property of S haemoglobin which leads to distortion and sickling of the erythrocyte at low oxygen tension depends on the very low solubility of the reduced form (Perutz and

Mitchison, 1950). A small difference in a peptide group between normal and S haemoglobins has recently been found (Ingram, 1956).

In recent years (*vide infra*), it has been realized that genetically mixed forms of "atypical" sickle-cell disease occur, one of the patient's parents possessing sickle-trait and the other some abnormal trait affecting haemoglobin or erythrocytes. Such cases are less severe than homozygous sickle-cell anaemia, but present in a wide variety of clinical forms (Smith and Conley, 1953, 1954).

Two typical cases are reported.

Case Reports

Case 1. Haemoglobin C Sickle-Cell Disease

The patient, a Jamaican negress aged 30, was seen at the Antenatal Clinic at Hammersmith Hospital in January, 1954 when she was 16-weeks pregnant. She had been resident in England since June, 1951.

In February, 1945, she had had a full-time normal confinement in Jamaica. After an apparently normal pregnancy she gave birth to a male infant, weighing 7 pounds 3 ounces, alive and well.

In January, 1953, she was admitted into another hospital following a 3-months incomplete abortion. Haemoglobin on admission was 48 per cent and splenomegaly was noted. She was transfused with 1 pint of whole blood. A form of sickle-cell anaemia was diagnosed at the time and confirmed by bone marrow puncture. Subsequent studies in Hammersmith Hospital (*vide infra*) revealed this was haemoglobin C sickle-cell disease.

In July, 1953, she had been seen at Hammersmith Hospital on account of incomplete abortion.

The uterus was curetted and recovery was uneventful. The haemoglobin was 82 per cent (12·1 g.). When next seen on 6th January, 1954, she was 16-weeks pregnant—last menstrual period 14th September, 1953. She looked healthy and had had occasional nausea during the first trimester but no morning sickness. There had been no other symptoms.

On examination, the patient was a healthy, well-developed negress. Her mucous membranes were of good colour, the breasts were active and well developed, and the lungs were clinically free from disease. Her abdomen was well covered, with the spleen 2 to 3 finger-breadths below the costal margin. The uterine fundus was 16 weeks in height, and there were no other relevant physical signs.

Urine—no abnormal constituents. Haemoglobin—81 per cent (11·6 g.). Blood group O Rhesus positive. Blood Wassermann and Kahn reactions—negative. X-ray of chest—no abnormality detected.

She was given Ferrous gluconate 0·3 g., b.d., and Vitaminoral capsules (vitamins A, B_1, C and D_3, Riboflavin and Nicotinamide) to take throughout the pregnancy. She attended the antenatal clinic at 4-weekly intervals. Progress was entirely satisfactory.

On 10th May, 1954, when she was 35 weeks by dates, she was admitted into the lying-in ward on account of the sudden onset of stabbing pains in both sides of the chest and dull aching pains in the right side of the abdomen. She looked ill, and writhed in bed on account of pain. The temperature was 100° F., the pulse 96/min., the respiration 24/min. Her eyes were blood-shot and the tongue was dirty, furred and dry. The respirations were rapid and shallow, and there was good air entry with some moist rales at the right base. The heart was normal, the blood pressure 100/65. The uterine fundus was 34 weeks in height and was not tender. The foetal heart was audible and regular. The spleen was palpable about 4 finger-breadths below the costal margin, and tender. There was no oedema.

Investigations

Haemoglobin 74 per cent (11 g.). Blood smear—few sickle-cells seen, but numerous target cells. Packed cell volume, 31 per cent, mean corpuscular volume, 97 cμ. mean corpuscular haemoglobin 34 $\mu\mu$g., mean corpuscular haemoglobin 35 per cent. White blood count 9,000 per c.mm. (polymorphs 7,560, lymphocytes 720/c.mm., monocytes 540/c.mm.). Bleeding time, 4½ minutes. Clotting time, 8 minutes. Prothrombin time, 12 seconds. Platelets 85,000 per c.mm. Sputum examination, *Strep. viridans* present. Culture—no tubercle bacilli. X-ray of chest—no evidence of pulmonary consolidation or deflation. X-ray of abdomen—single foetus. Vertex, R.O.A. Maturity—36 weeks. No abnormality.

Complete bed rest was ordered and she was given a light diet supplemented by oral vitamins and ferrous gluconate. The temperature remained elevated between 99·4° F. and 102·2° F. Penicillin 250,000 units 6-hourly was given intramuscularly for 10 days in view of the clinical signs of pulmonary infection.

On 15th May, 1954 further examination of the chest showed signs of friction in the right base together with minimal effusion. On the 18th May, diagnostic aspiration of the right pleural cavity was performed and 0·5 ml. opalescent brownish fluid was obtained. The penicillin dosage was increased to 500,000 units six-hourly.

An X-ray examination of the chest on 23rd May revealed a small patch of consolidation at the right base. There was no pleural effusion. The pyrexia was subsiding (temperature 99° F.) and she maintained a steady progress until 3rd June, 1954, when she had a false labour lasting 10 hours. In view of the known dangers of pregnancy complicating sickle-cell disease, the patient was advised to remain in hospital up to the time of delivery.

On 20th June, 1954 (duration of pregnancy—40 weeks) she went into labour and was delivered of a healthy male infant weighing 6 pounds 6 ounces. Labour lasted 5 hours 10 minutes and blood loss was minimal.

On 21st June (2nd day of puerperium) she developed puerperal pyrexia ranging between 101° F. and 99° F. for 7 days. She was treated with 500,000 units of penicillin and 0·5 mg. ergometrine twice daily by mouth for 5 days.

Nasal, throat, and vaginal swabs, and a catheter specimen of urine were taken for bacteriological examination. These yielded no organisms. The lochia were not offensive. The chest was clinically clear, and, apart from the splenomegaly already noted, physical examination revealed no other abnormality.

The haemoglobin estimation on 24th June, 1954 was 55 per cent (8·1 g. per ml.).

On 28th June the pyrexia had subsided and the general condition was satisfactory. Lactation was well established. Postnatal examination on the 10th day revealed no pelvic abnormality. The spleen was still palpable but not tender. On 2nd July, 1954, she was given 4-weeks supply of ferrous gluconate (gr. 5 b.d.) and discharged together with her baby.

On 26th July, 1954, she was again seen at the postnatal clinic. She felt well and had no complaints. The baby was gaining weight satisfactorily and was still breast fed. Her general condition was good, the chest was clinically clear, the spleen was still enlarged and pelvic examination revealed no abnormality.

Haemoglobin—78·5 per cent (11·1 g.) per ml.

Case 2. Sickle-cell Trait

A negress, aged 34 years, para-2, had been married 11 years. She had lived in the United Kingdom since coming from Trinidad in 1949.

She first attended the Antenatal Clinic on 9th June, 1954, when she had a normal 10-weeks pregnancy.

She had had measles at 6 years, jaundice at 7 years, and whooping cough when aged 14 years. For the last 15 years she had had colds associated with wheezing. There was no relevant family history.

On examination, her general condition was good. The blood pressure was 125/80.

Urine—no abnormality. Haemoglobin 78 per cent (11·5 g.). Blood Wassermann and Kahn—negative.

She was referred to her County Council Antenatal Clinic, which she attended regularly every 4 weeks.

In August, 1954, she had nasal catarrh followed by bronchitis with productive cough. Persistent wheezing and slight bronchospasm were found when she attended the Antenatal Clinic on 21st September, 1954 (24-weeks pregnancy). A diagnosis of asthma and bronchitis was made. The chest X-ray revealed no abnormality.

Sputum—*Streptococcus pneumoniae* and *Strep. viridans*. Haemoglobin 72 per cent (10·7 g.). White blood cells 9,000 (polymorphs 83 per cent; eosinophils 5 per cent; lymphocytes 9 per cent; monocytes 3 per cent).

On 6th October, 1954 (27-weeks pregnant), she complained of a bearing-down feeling and occasional stress incontinence, and was found to have a cystocoele and rectocoele. A large ring pessary was inserted. The ring was removed after 5 weeks.

On 1st November, 1954, she was still wheezing, 12 weeks after the original asthmatic attack. Out-patient treatment with aureomycin and penicillin produced no improvement, and she was admitted for further treatment on 12th November. She was 6-months pregnant. There was severe bronchospasm. The chest X-ray was normal.

Blood pressure 120/70. Urine—normal. Sputum—culture yielded a few colonies of *Strep. pneumoniae* and *Strep. viridans*, both sensitive to penicillin. Haemoglobin 70 per cent (10·3 g.). White blood cells 4,000 (polymorphs 68 per cent; eosinophils 9 per cent; lymphocytes 16 per cent; monocytes 7 per cent).

Intensive anti-spasmodic treatment with 1 per cent Isoprenaline by inhalation and ephedrine gr. ¼, t.d.s., was successful, and she was discharged on 4th December, 1954, to continue treatment at home.

Obstetrically the progress remained satisfactory. On 19th January, 1955, she was admitted in labour and delivered spontaneously of a healthy female infant. Labour lasted 6 hours and 50 minutes. The child weighed 8 pounds 1 ounce.

After delivery, the haemoglobin was 57 per cent (8·4 g.), and further haematological investigation was carried out:

Red blood count 3·5 millions. Packed cell volume 28 per cent. Mean corpuscular volume 80 cu.μ. Mean corpuscular haemoglobin concentration 30 per cent. Reticulocytes 1·5 per cent. Plasma not icteric. The red cells sickled slowly on reduction.

The blood film exhibited marked anisocytosis, moderate anisochromasia and frequent poikilocytosis of red cells. Polychromasia, hypochromasia and target cells were present. From the results of these investigations, and from the special tests (*vide infra*), it was concluded that co-existence of sickle-cell trait and iron-deficiency anaemia was probably responsible for the blood picture.

She was treated by 50 mg. and 4×100 mg. of intravenous iron as Ferrivenin during the following week, and ferrous gluconate 0·3 g., t.d.s. The blood picture now indicated rapid regeneration, and the reticulocytes rose to 8 per cent. She was discharged home on 29th January, 1955.

Special Methods of Haematological Investigation

Heparinized venous blood samples were used for the standard haematological procedures, and for preparation of concentrated HbO_2 and HbCO solutions for the special investigations.

Sickling

Drops of blood were mixed with buffered, isotonic sodium dithionite (Itano and Pauling, 1949) and sealed between slide and cover-glass. Observation was made after a few minutes, and after 24 hours at room temperature and at 37° C.

The birefringence of the sickled cells could be measured with a sensitive rotating compensator (Perutz and Mitchison, 1950).

Paper Electrophoresis

Ten per cent solutions of HbCO were subjected to electrophoresis on Whatman No 1.

horizontal paper strips for 18 hours at 300 volts and 2 milliamps per paper, using pH 8·6 Barbitone buffer of ionic strength 0·05. The strips were 9 cm. wide, and a known marker was run alongside the test. The papers were then dried in the air, and the separated haemoglobins were directly visible. Photographic records were made by transmission of violet light (Fig. 3), and the patterns could be scanned by the recording photometer of Laurence (1954) and evaluated quantitatively. For discussion of the electrophoretic analysis of haemoglobin the reader is referred to articles by White and Beaven (1954), and White, Beaven and Ellis (1956).

Solubility of Reduced Haemoglobin

This was carried out in strong phosphate buffers at pH 6·7 (Jope and O'Brien, 1949; Perutz and Mitchison, 1950), using small, closed tubes set up in an atmosphere of nitrogen and equilibrating for 5 days (Beaven and White, 1953; Humble, Anderson, White and Freeman, 1954).

Results

Case 1. Haemoglobin C Sickle-Cell Disease

Except at the time of her abortion in 1953, and after delivery in June, 1955, the blood count has remained at 3·5–4 million red cells, haemoglobin 70–86 per cent (10·3–12·7 g./100 ml.), with normal mean corpuscular volume and mean corpuscular haemoglobin concentration. Target cells have always been numerous in the blood smear (Fig. 1), and occasional sickle-cells present. Sickling occurs very readily on reduction of venous blood, and finger-prick blood after constriction with a rubber-band for 3 minutes contains numerous sickles. After 24 hours, a sickled preparation contains predominance of slender, elongated forms (Fig. 2) with high absolute birefringence—0·0027 at 599·6 mμ. The reticulocytes range from 3 to 8 per cent, and the plasma bilirubin is about 1 mg./ml.

The osmotic resistance of the red cells is increased, the fragility curve being deviated to the left and 50 per cent haemolysis occurring at 0·32 per cent sodium chloride.

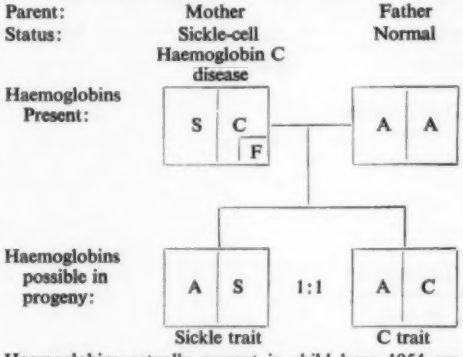
Electrophoretic analysis on paper shows that no normal haemoglobin is present, but a mixture of sickle-cell haemoglobin (Hb S, 53 per cent) and haemoglobin C (47 per cent). This electrophoretic pattern has been noted by Smith and Conley (1953) and Larson and Ranney (1953). Six per cent of foetal haemoglobin has been detected by a sensitive combined denaturation and U.V. spectrographic technique (Beaven, Ellis and White, 1956).

The solubility of the reduced haemoglobin is low, 1·32 g./litre at ionic strength 4·75 in pH 6·7 phosphate buffer. This is at the lower limit of the solubility found in sickle-trait, and higher than for pure sickle-cell anaemia, with excess of Hb S present.

Familial Studies

The patient's Jamaican husband is not anaemic, his red cells do not sickle, and no abnormal haemoglobin is detectable by electrophoretic and solubility studies.

The baby born in June, 1954, has been studied at intervals since. He is not anaemic, the blood film shows target cells, but there is no sickling. Foetal haemoglobin has gradually disappeared over the first four months of postnatal life, and been replaced by a mixture of adult, normal haemoglobin (A) and haemoglobin (C) as revealed by paper electrophoresis. He therefore carried the C-trait. The genetic relationships are shown in Figure 3, and the electrophoretic



Haemoglobins actually present in child born 1954 are A+C=C trait.

Fig. 3

Genetic relationships in Jamaican family, in which the mother has sickle-cell haemoglobin C disease. Normal, adult haemoglobin=A; Foetal haemoglobin =F; Sickle haemoglobin=S; Haemoglobin C=C.

patterns for the family in Figure 4. A number of reports are now available on the clinical manifestations of the combined inheritance of haemoglobins S and C (Itano and Neel, 1950; Kaplan, Zuelzer and Neel, 1951, 1953; Ranney, Larson and McCormack, 1953; Edington and Lehmann, 1954).

Case 2. Sickle-cell Trait

This patient was fairly anaemic immediately post-partum, with hypochromic target cells in the film. Red blood cells, 3·5 million; haemoglobin 57 per cent (8·4 g.); mean corpuscular volume 80 cu.μ; mean corpuscular haemoglobin concentration 30 per cent; reticulocytes 1·5 per cent, bilirubin normal. Osmotic resistance was at the upper limit of normal.

Oral iron therapy produced a reticulocyte response of 8 per cent and rise of blood count over two months to: Red cells, 4·5 million; haemoglobin 79 per cent (11·6 g.); mean corpuscular volume 86 cu.μ; mean corpuscular haemoglobin concentration 30 per cent; reticulocytes 3 per cent.

Her red cells sickle slowly on reduction, producing many broad, "holly-leaf" forms with low birefringence (0·0006 at 599·6 mμ). The electrophoretic pattern indicates a mixture of normal haemoglobin (A, about 55 per cent) and sickle-cell haemoglobin (S), as found in sickle-cell trait.

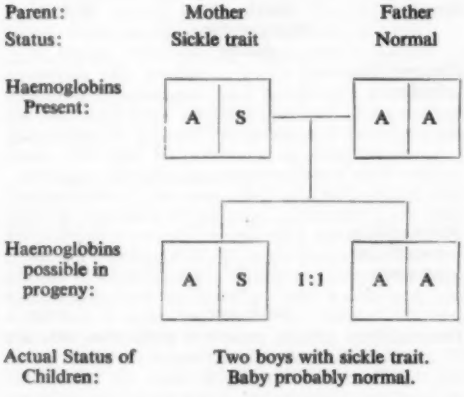


Fig. 5

Genetic relationships in Trinidad family, in which the mother has sickle-cell trait.

Familial Studies

The patient's husband from Trinidad has a normal blood picture, and his haemoglobin appears normal. Two elder children each carry the sickle-cell trait, like the mother. The baby has been followed through early infancy, and the electrophoretic pattern at 11 weeks of age suggests that the foetal haemoglobin is being replaced by normal A haemoglobin only and that the child does not have the trait. The genetic and biochemical relationships are shown in Figures 5 and 6.

Discussion

Pathogenesis

The essential pathological condition which causes sickling of the erythrocytes is now known to be due to the presence within them of the abnormal haemoglobin S. This type of haemoglobin is far less soluble than normal haemoglobin in the reduced state.

Sickle-cell disease is an inherited condition, and the presence or absence of the sickling phenomenon appears to be determined by a single gene. The child who receives this gene from one parent and a normal gene from the other develops the sickle-cell trait (heterozygous state), but does not usually exhibit symptoms and does not become anaemic. On the other hand the child who inherits the genes for sickling from both parents develops sickle-cell anaemia (homozygous state). Occasionally sickle-cell anaemia may be found in a child although the erythrocytes of only one of its parents sickle *in vitro*. Neel (1952) suggested that the most likely explanation was that the apparently normal parent had contributed another gene, which in combination with a sickle-cell gene produced an overt sickle-cell anaemia.

A number of types of haemoglobin have now been distinguished, apart from normal haemoglobin (A) and foetal haemoglobin (F). Electrophoretic studies have distinguished S, the sickling type, and also C, D, E, G, H, I, etc. These are genetically determined, and in some cases may interact with the sickle-cell gene to produce distinct anaemia.

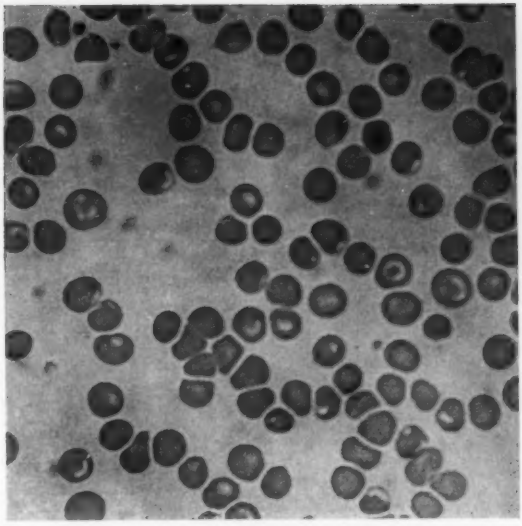


FIG. 1

Photomicrograph of blood smear of Jamaican woman with sickle-cell haemoglobin C disease, showing target cells. 3 mm. Zeiss Apochromat. Magnification ×900.

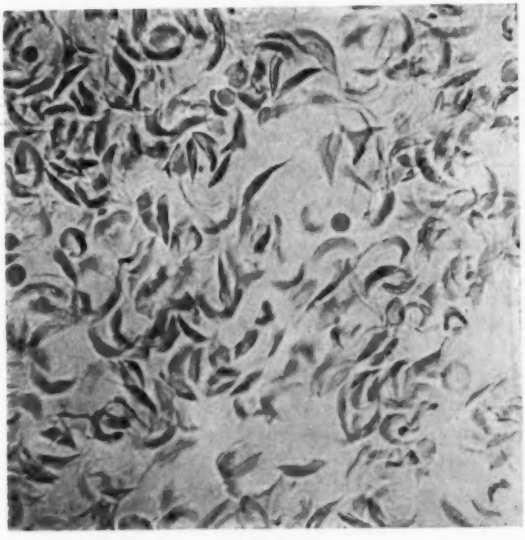


FIG. 2

Photomicrograph of a sickled, wet preparation of the blood of Patient 1. The sickles are slender, with filamentous processes. 3 mm. Zeiss Apochromat. Magnification ×900.

R.H.O.B., J.C.W. [686]

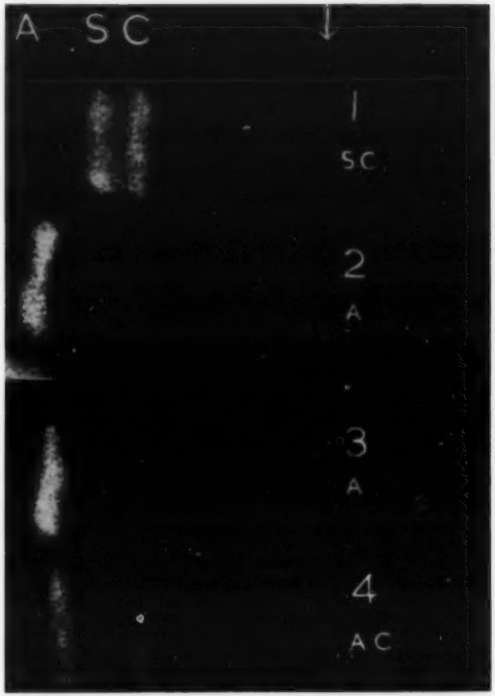


FIG. 4

Transmission photograph in violet light of the paper electrophoresis patterns of the Jamaican family to which Patient 1 belongs.

1. Mother; sickle-cell haemoglobin C disease.
2. Father; normal.
3. Normal control.
4. Baby at 4 months of age; C-trait.

Arrow indicates origin. Cathode on right.

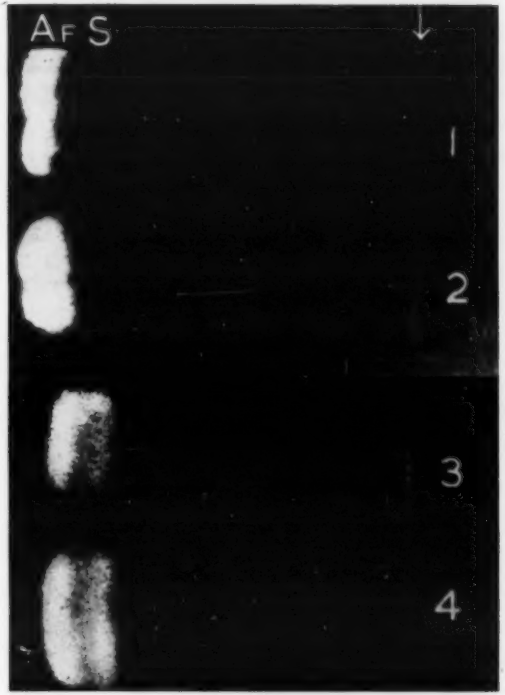


FIG. 6

Transmission photograph in violet light of paper electrophoresis patterns in Trinidad family, in which the mother has sickle-cell trait.

1. Father, normal.
2. Infant, aged 11 weeks. Adult haemoglobin with 35 per cent foetal haemoglobin (determined by alkali-denaturation) incompletely resolved.
3. Mother, sickle-cell trait.
4. Eldest child, sickle-cell trait.

Arrow indicates origin. Cathode on right.

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Briefly, C is electrophoretically different from A but has a normal solubility in the reduced form. D is indistinguishable from S electrophoretically, but unlike it has a normal solubility in the reduced form. A combination of these haemoglobins with sickle-cell haemoglobin appears to explain many of these atypical sickle-cell anaemias. Several possible combinations are now recognized (Smith and Conley, 1954; Itano, Bergren and Sturgeon, 1956):

(1) A combination of haemoglobins S and C in haemoglobin C sickle-cell disease (i.e., the subject has inherited one gene for haemoglobin S formation from one parent, one for haemoglobin C from the other).

The clinical picture is largely that of sickle-cell anaemia, though milder, and the disease follows a relatively more benign course. This is of particular interest since Case No. 1 is of this type. There is a definite tendency to develop thrombotic lesions, due to impacted masses of sickled cells, in many parts of the body (Smith and Conley, 1953, 1954).

(2) A combination of sickle-cell haemoglobin and haemoglobin D (i.e., one gene or sickle-cell haemoglobin and one gene for haemoglobin D) (Sturgeon, Itano and Bergren, 1955; White and Beaven, 1954; Stewart and MacIver, 1956).

(3) Microdrepanocytic disease, a combination of sickle-cell and thalassaemia disease (i.e., one gene for sickle-cell haemoglobin and one gene for thalassaemia or Mediterranean anaemia). This is a fairly severe condition, encountered not infrequently in Southern European and Middle-Eastern countries bordering the Mediterranean, as well as in American negroes (Silvestroni and Bianco, 1952; Powell, Rodarte and Neel, 1950; Humble *et al.*, 1954).

(4) Congenital spherocytosis–sickle-cell disease (inheritance of genes for acholuric jaundice and for sickling (Smith and Conley, 1954)).

Pregnancy

The number of reported cases of sickle-cell anaemia and associated conditions in pregnancy is small. The sickle-cell trait is commonly met with in the pregnant African woman, but sickle-cell anaemia is much less common since a high percentage of those affected appear to die in childhood. Most of the reported cases are from the Negro population of the U.S.A. where the condition has been closely studied. Sydenstricker (1924) first mentioned the association of pregnancy and sickle-cell anaemia but it was not until 1941 that Kobak, Stein and Daro made the first detailed analysis of the effects of this condition on pregnancy. The total number of cases recorded up to 1950 was 146 (Beacham and Beacham, 1950). Many cases must, however occur which are not reported, and this is probably true of the African Continent.

Sodeman and Burch (1938) stated that there was decreased fertility in the female with sickle-cell disease. They based their conclusion on the literature of that time which showed that, of 15 women of known parity, 10 were pregnant for the first time and, of the remaining 5, only 3 had more than one child. It has also been stated that genital hypoplasia sometimes occurs in those patients who reach maturity. One of Kobak's cases, however, was pregnant for the seventh time. Killingsworth and Wallace's (1936) patient died as a result of her 12th pregnancy. The impression of one of us (R.H.B.), working in Ghana, is that the fertility rate is not as markedly reduced as has been suggested, but in any case chronic debilitating anaemia would appear to diminish fertility to a certain extent.

It appears there is a definite tendency for the mother with sickle-cell anaemia to abort. In 48 cases reviewed from the literature by Margolies (1951), 15 had a history of one or more abortions. Beacham and Beacham (1950), from 60 pregnancies from the Charity Hospital, New Orleans, found 8 abortions (16 per cent) and compared this with the abortions in 96 cases in the literature (15 per cent). It appears, therefore, that 15–20 per cent of these patients abort. According to Brews (1953) about 20 per cent of all pregnancies terminate in abortion, but it should be remembered that some of these are induced, so that it would seem that the abortion rate is increased, though perhaps not so markedly as has been believed.

It is certainly clear that pregnancy has no beneficial effects on the disease. Indeed it is probable that pregnancy renders the patient more likely to acute episodes. Crises are common though the symptoms may be confusing. The complications of pregnancy and maternal

mortality rate are high in sickle-cell anaemia. Many exhibit signs of pre-eclamptic toxaemia and even eclampsia. In Beacham and Beacham's (1950) series 22 per cent were considered to have pregnancy toxaemia. Margolies (1951) reviewed 7 toxaemic patients in 35 pregnancies (20 per cent). It should be remembered that features which mimic toxaemia may be in fact manifestations of the disease. Oedema may be a complication of profound anaemia, and a haemolytic crisis with neurological involvement can stimulate an eclamptic fit. In Beacham and Beacham's (1950) series 46 per cent exhibited urinary tract infection, 19 per cent respiratory infections, 19 per cent puerperal sepsis; and 1 in 5 mothers died while classified as an obstetric patient. The causes of death are principally haemolytic crises, embolic phenomena, sepsis and sudden cardiac failure.

It should be emphasized that these risks do not apply so much to the sickle-cell trait, but may be of considerable importance in the cases of intermediate severity, where the sickle gene combines with another abnormally-expressed gene, such as haemoglobin C. Thus, Smith and Conley (1954) found pregnancy to be more hazardous in women with haemoglobin C sickle-cell disease than in sickle-cell anaemia. Edington (1955) has reported that, among 13 women whose blood sickled and who died suddenly in the last three months of pregnancy, neither sickle trait nor homozygous anaemia was present in a number of the cases, and at least one suffered from haemoglobin C sickle-cell disease.

Treatment

There is at present no specific therapeutic agent available for the treatment of the disease. The management of these patients is that of optimum obstetric care, and they should be seen frequently during the antenatal period. Every effort should be made to improve their general state of health and particular attention should be paid to their nutritional requirements, since most of them have faulty diets due to their economic status.

Iron and vitamins are advised in as much as an iron-deficiency anaemia may be present. Oxygen therapy, vasodilator drugs, transfusion, A.C.T.H. and splenectomy have all been employed (Dacie, 1954). Mepacrine, liver extract, and iron have been used and are of some value where the picture is complicated by malaria or nutritional deficiencies. Pure oxygen is of value in an emergency and during labour. Blood transfusions are of temporary value and in severely anaemic patients a transfusion may be life saving. This is particularly valuable in antepartum and post-partum haemorrhage. Splenectomy has been done sporadically for 25 years, but on the whole the results have been disappointing.

Because of the thrombotic episodes in a "crisis" anticoagulant therapy was tried by Murphy and Shapiro (1946). Heparin was used but the crises became more intense, the mechanism of the thrombotic phenomena being different from ordinary thrombus formation. Inhibition of sickling by Tromexan (ethyl biscoumacetate) has been reported by Griffiths (1955), but not confirmed in 4 cases with sickle-cell trait by Tulloch and Stuart (1956).

Methylene blue, as an oxidant, has been tried without effect. In 1952 Sass reported dramatic symptomatic improvement following the use of A.C.T.H. in a patient suffering from sickle-cell anaemia. No significant change took place in the blood picture, and it is doubtful whether A.C.T.H. or cortisone has any real place in the treatment of sickle-cell disease.

Delivery should be conducted so as to avoid trauma, anoxia, blood loss, and infection. Local anaesthesia and analgesics such as pethidine hydrochloride have proved particularly useful. Blood should be cross matched ready for transfusion at very short notice. Beacham and Beacham (1950) advocate a slow transfusion during labour. Because of the increased risk of infection prophylactic administration of antibiotic agents is advised in these cases.

Summary

Two cases of sickle-cell disease and pregnancy are described.

Case 1 showed certain features of particular interest, and was an example of haemoglobin C sickle-cell disease. The patient's general condition appears to have deteriorated during pregnancy. She complained of typical joint and muscle pains met with in the exacerbation of

sickle-cell disease. The chest lesion was probably an embolic rather than a pneumonic phenomenon.

Case 2 showed no features peculiar to the sickle-cell trait during the antenatal period—her haemoglobin level varied between 70 per cent and 80 per cent. She became fairly anaemic immediately post-partum and with a haemoglobin level of 57 per cent (8·4 g.). Oral and intravenous iron therapy over a period of two months raised the haemoglobin level to 79 per cent (11·6 g.).

It is clear that pregnancy has no beneficial effects on the disease, and probably renders the patient more likely to acute episodes.

Sickling should be tested for in the antenatal period, but further studies are needed for full elucidation of sickle-cell anaemias, including paper electrophoresis. Methods of haematological investigation are described in detail together with the results of Familial studies.

Treatment is mainly that of optimum obstetric care and is essentially symptomatic.

Acknowledgments

Our thanks are due to Professor J. C. McClure Browne, under whose care the patients were admitted, for permission to publish these cases.

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A STATISTICAL EVALUATION OF THE NITROGLYCERINE FLICKER-FUSION THRESHOLD TEST AND THE "WEIGHT-GAIN SIGN" IN THE PREDICTION OF THE CLINICAL SYNDROME OF PRE-ECLAMPSIA

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THIS work set out to test the prognostic significance attributed to the Nitroglycerine Flicker-Fusion Threshold Test (N.F.F.T.) by Brill *et al.* (1951, 1952) and to excessive 20–30 week primigravid weight-gain by Hamlin (1952, 1953) in pre-eclampsia.

It was also intended to compare their sensitivity, specificity, and practicability as prognostic measures, and to fit them, if valid, into the scheme of a large-scale enquiry into the aetiology and management of toxaemia.

Corroboration by Marty and Hardy (1952) and refutation by Morris, Tomkinson and O'Connor (1953) and by Gillim (1954) of Brill's findings emphasized the need for a further check.

METHOD

The Flicker-Fusion Threshold (F.F.T.), as its name suggests, can be defined as the minimum number of cycles per second at which the separate flashes of a flickering light source appear to fuse into a steady light. Being optimal under conditions of normal vascular tone it is adversely affected by both vasospasm and vasodilatation. If administration of the vasodilator, nitroglycerine, to a test subject reduces the F.F.T., normal tone is presumed to have existed, ability to discern flicker having been impaired by the congestion caused by the vasodilator—a negative test. On the other hand an increase in the F.F.T. after nitroglycerine is taken to denote a state of vasospasm relieved by the vasodilator thus improving perception—a positive test.

Its use as a prognostic test in toxaemia depends on the assumption that this alleged "pre-hypertensive" increased vascular tone nearly always progresses to overt hypertension of pregnancy.

The instrument used for measuring the F.F.T. was based on the then unpublished circuit diagram of Morris *et al.*, varying only in detail and in that it was calibrated, and later checked, against the highly accurate and stable Daws low-frequency oscillator. Their claims about the stability of this Flicker-meter are endorsed.

As originally suggested by Krasno and Ivy (1950) and as repeated by Brill *et al.* the patient was seated at a distance of 1·6 metres from the light source. Precautions recommended by all authors prior to, and during testing were taken, namely, that patients must not have had any sedative or vasodilator drug or tobacco for 6 hours, or alcohol for 24 hours prior to the test; that they must have rested at least 10 minutes before the test; that lighting must be uniform and that the machine must not be moved

throughout the test; that noise be reduced to a reasonable minimum, and that the patient be comfortable and fully aware of the absence of any competitive element in the test.

A "run" consisted of lowering the frequency of the light source by turning a knob over a dial marked in cycles per second until the subject indicated the point at which flicker appeared.

Runs were begun at different levels on the dial to avoid habit, or timing of replies by the subject.

Nitroglycerine gr. 1/100 in a tablet with a chocolate base was used since it was found that, although lactose-base tablets shortened the duration of the test, they were more liable to induce fainting or a feeling of faintness sufficient to cause abandonment of the test—presumably because of the quicker absorption of nitroglycerine. A sensation of warmth, mild sweating, and slight throbbing in the head were common but easily tolerable side-effects. Actual headache was much less frequent.

Preliminary studies on the reliability of the F.F.T. and the possible effect of eye-fatigue showed that once a normal subject (pregnant or non-pregnant) had settled, after a few runs, at a certain level, she could continue with no significant variation for up to 35 readings in rapid succession. The deviation in the average of each successive group of 10 readings ranged from 0·05 to 0·2 cycle per second, the latter being entirely confined to the third groups of 10. The highest number of readings in a single test in the series proper was 26 (16 before and 10 after nitroglycerine), the second highest being 21, all with an interval of up to 2 minutes between them.

While a large number of cases could be decided on 5 runs at two-minute intervals, or 10 runs at one-minute intervals after the nitroglycerine, all eventualities were covered by 10 readings at two-minute intervals.

All authors regard as significant a minimum alteration in the F.F.T., following the nitroglycerine, of 0·5 cycle per second; but a pilot survey indicated that on this basis more than a quarter of the results were ruled "equivocal".

From these preliminary trials the following test system was adopted:

(1) A series of trial runs until 3 successive readings were exactly the same—the last being taken as the F.F.T.
(2) Nitroglycerine gr. 1/100 in a chocolate base tablet placed under the subject's tongue—not chewed.
(3) Interval of two minutes.
(4) Ten readings at two-minute intervals—the average reckoned and any increase or decrease in the F.F.T. deemed a "positive" or "negative" N.F.F.T. test accordingly.

Patients were included without selection as they came under observation at antenatal clinics serving Southmead Hospital, and in the wards of the Professorial Unit at Southmead. Rather less than half of them were seen at a special "Weight-Gain" clinic to which they were referred primarily for a therapeutic trial, which was proceeding at the same time. This clinic was supplied largely with patients from the above-named antenatal clinics, the exceptional cases being excluded from the series.

Each of these clinics has one set of scales none of which has been changed during this survey. Each patient has been weighed on one scale throughout her pregnancy or at least its relevant part.

The basic pattern of Flicker-testing has been a first test at under 20 weeks, and a third after 30 weeks; but this procedure has not been a rigid one so that many subjects have had four, and a few five.

Toxaemic patients, who were selected as "positive controls" have had in the main single tests.

The definition of toxaemia for purposes of this investigation has been a single rise to a diastolic pressure of 90 mm. Hg or above (with or without oedema or albuminuria) occurring for the first time at 24 weeks or later. When the early pregnancy blood pressure was unknown it had to be repeated or maintained, or be accompanied by oedema (or albuminuria).

This has allowed the inclusion of those cases which, having sustained a rise to 90 mm. Hg diastolic, responded immediately to routine antenatal salt and diet restriction; thus reducing the bias against the correct prognostication of toxaemia which such routine interference might introduce.

Results

Flicker Tests

Discounting preliminary tests a total of 231 flicker tests have been done on 136 patients. They comprise the following:

102 expected negative tests (in which the blood pressure was normal).
39 expected positive tests (in which there was a raised blood pressure, cardiovascular or renal disease, or a history of previous toxaemia).
2 unexpected negative tests (in which the blood pressure was raised).
2 equivocal tests (in which there was no alteration in the F.F.T. after nitroglycerine).
86 unexpected positive tests (in which the blood pressure was normal, and there was no cardiovascular or renal disease, or history of previous toxaemia).

This last group consists of those who, according to Brill *et al.*, should later develop clinical signs of pre-eclamptic toxaemia.

Discarding those whose pregnancy was still continuing and those whose records were inadequate there remain 94 cases which comprise the series proper.

The term "forecast" being used to cover the alleged association of a positive test with pre-eclampsia, and a negative test with its absence, the results are shown in Table I.

It will be seen from Table I that in the positive forecast group 36 were correct and 15 incorrect, while in the negative forecast group there were 26 correct and 17 false, making a total of 62 correct and 32 incorrect forecasts.

Statistical appraisal and comparison with the results of the weight-gain group follows Table II below.

In Brill's series 52 patients out of 57 showing unexpected positive tests developed toxaemia, the remaining 5 being up to then undelivered—an incidence of correct forecasts of not less than 91 per cent, as against 36 out of 51 (70·5 per cent) in the comparable group in this series.

The incidence of correct negative forecasts of 60·5 per cent compares with an incidence of 96·7 per cent reported by Marty and Hardy.

Weight Gain

A number of writers particularly Dawson and Borg (1948), Dieckmann, Smitter and Rynkiewicz (1952) and Dawson (1953) stress the association of excessive weight-gain over a specific period of pregnancy (as opposed to

TABLE I

Flicker Test	No. Developing Toxaemia			No. Not Developing Toxaemia		
	1st Group	2nd Group	Total	1st Group	2nd Group	Total
Positive "forecasts" ..	20	16	36	8	7	15
Negative "forecasts" ..	15	2	17	23	3	26
			53			41

TABLE II

Weight Gain	No. Developing Toxaemia			No. Not Developing Toxaemia		
	1st Group	2nd Group	Total	1st Group	2nd Group	Total
Positive "forecasts" ..	25	11	36	10	7	17
Negative "forecasts" ..	1	3	4	2	3	5
			40			22

excessive total weight-gain) with pre-eclamptic toxaemia.

The first-named investigators showed that this relationship is much closer during the last four weeks before term or termination, while the second-named indicated a significant increase of toxaemic over normal weight-gain as early as the thirteenth to the twentieth week.

Hamlin, reporting a remarkably successful attack on eclampsia and severe pre-eclampsia apparently by weight-gain control, affirmed that, "Approximately 90 per cent of normotensive or hypotensive primiparae who have this early weight-sign (a gain of over 8 pounds between 20–30 weeks) develop pre-eclampsia (mild or severe) by term or during labour"; and conversely that, "if such a patient does not increase her weight by more than 8 pounds in those critical weeks she will not, in the vast majority of cases, have pre-eclampsia".

Primigravidae demonstrating this weight-sign were designated "positive forecasts", while those gaining 8 pounds or less between 20 and 30 weeks were termed "negative forecasts". All primigravidae in this group of 62 were included, since age was shown to exert no significant influence on these forecasts—due perhaps to the small numbers involved.

Table II shows the total number of correct forecasts to be 41, and of incorrect forecasts 21.

Statistical Analysis and Comparison

For the purpose of statistical analysis we arrange the results as in Table III.

The comparison of the number of tests which were correct in their prediction with those which were incorrect will give some idea of the reliability of the two tests and of the possible advantages of one over the other. This will also give an answer about the sensitivity of the test methods. We first find that for the Flicker test the percentage of correct forecasts was in the 1st and 2nd group 65 per cent and 68 per cent respectively, and in the total 66 per cent, and consequently that of incorrect forecasts 35 per cent, 32 per cent, and 34 per cent respectively. The stability of the percentage of correct forecasts from group to group is quite obvious. However, to make quite certain that the apparent agreement can also be regarded as statistically significant, the standard error (St.E.) of the percentage of correct results has been calculated and in each case is considerably less than half the observed difference between correct and incorrect forecasts.

In the case of primigravidae only, we find 68·4 per cent and 66·6 per cent in Group I and II respectively and 67·7 per cent in the total, and consequently for incorrect forecasts 31·6 per cent, 33·5 per cent, and 32·3 per cent. The percentages for the two groups, correct and incorrect, although not precisely the same, are sensibly of the same magnitude as those for all cases, and the standard error of these percentages shows again that we may expect in a greater number of cases about two-thirds of correct results, that is of correct forecasts of toxaemia.

Going now over to the Weight-Gain Test we find the percentages of correct results for the two groups and the total to be 71 per cent, 58·3 per cent, and 65·5 per cent respectively, and consequently those for the wrong forecasts 29 per cent, 41·7 per cent, and 34·5 per cent. These percentages are in the same order of magnitude as the percentages for the two groups of correct and incorrect forecasts which we find for the Flicker Test. The calculation of the standard errors shows again that the difference between the number of correct and incorrect forecasts may be regarded as statistically significant (except for the 2nd group where the difference is only little more than 1½ times the standard error) and therefore an estimate of roughly two-thirds correct forecasts is justified.

We have thus found a similar percentage of correct forecasts for the Flicker Test and for the Weight-Gain Test. It was roughly two-thirds of all the tests carried out. The similarity in percentage of correct forecasts, however, does not mean that the same test results always occur in the same individual and the question in which we are now interested is to what extent the test results coincide in particular individuals. The observed coincidence can be seen from Table IV. We first notice that $36/55 = 65$ per cent of cases showed a coincidence of either correct or wrong test results, and consequently a percentage of 35 per cent had conflicting test results. In order to assess whether the results between the two

TABLE III
Statistical Analysis and Comparison

	1st Group		2nd Group		Total	
Flicker Test: All cases:		Per cent		Per cent		Per cent
Correct+ "forecasts"	20		16		36	
Correct− "forecasts"	23		3		26	
Total correct "forecasts"	43	65	19	68	62	66
Wrong+ "forecasts"	8		7		15	
Wrong− "forecasts"	15		2		17	
Total wrong "forecasts"	23	35	9	32	32	34
	*St.E. 5·86		St.E. 8·8		St.E. 4·9	
Flicker Test: Primigravidae only:						
Correct+ "forecasts"	14		15		29	
Correct− "forecasts"	12		3		15	
Total correct "forecasts"	26	68·4	18	66·6	44	67·7
Wrong+ "forecasts"	4		7		11	
Wrong− "forecasts"	8		2		10	
Total wrong "forecasts"	12	31·6	9	33·4	21	32·3
Weight Gain: Primigravidae only:						
Correct+ "forecasts"	25		11		36	
Correct− "forecasts"	2		3		5	
Total correct "forecasts"	27	71	14	58·3	41	65·5
Wrong+ "forecasts"	10		7		17	
Wrong− "forecasts"	1		3		4	
Total wrong "forecasts"	11	29	10	41·7	21	34·5
	St.E. 7·36		St.E. 10·0		St.E. 6	

* Standard Error.

tests on the identical persons were more conflicting than is compatible with mere chance fluctuations the Chi-square Method may be applied. Chi-square, calculated with correction for continuity, results as 1·98 which means that the difference observed could arise with a fairly high probability, and we have, therefore, no reason for assuming that the two tests measured essentially different things.

The analysis so far has been concerned with the sensitivity of the tests. Of no less importance is the question of how unspecific the tests are.

That there is a considerable degree of unspecificity in both Flicker and Weight Test, can be seen by looking at Table I. For example of the 28 predictions of toxaemia by the Flicker Test in Group 1, 8, that is 28 per cent, were incorrect and of the 38 predictions of non-toxaemia 15, that is 39 per cent, were wrong. The assessment of the unspecificity of the tests seems therefore indicated. For this purpose we proceed as follows according to a method explained below.

The sensitivity of the Flicker Test according to our sample results (all cases, column 3 of Table I) are as follows:

Flicker		*Sample*	
Toxaemia	Test+	36	69 per cent
	Test−	17	31 per cent
Non-toxaemia	Test+	15	36·6 per cent
	Test−	26	63·4 per cent

TABLE IV

	Flicker Test			
	Correct+	Correct−	Wrong+	Wrong−
Weight Gain:				
Correct+	25			6
Correct−		2	2	
Wrong+		8	8	
Wrong−	3			1

For the purpose of carrying out the statistical test, the table was collapsed into the following 2×2 table (Table V) according to the correct and wrong results for both tests.

TABLE V

	Flicker Test		
	Correct	Wrong	Total
Weight Gain:			
Correct ..	27	8	35
Wrong ..	11	9	20
Total ..	38	17	55

In order to take both sensitivity and specificity of the test duly into account, the results of a small sample test must be seen against the background of the incidence of toxaemia in the population of pregnancies. From the records of Southmead Hospital and of the Public Health Department for Bristol a tentative estimate was made of the incidence of toxaemia in the population of Bristol and district, namely, 11·4 per cent. Thus 88·6 per cent were reckoned as not being liable to toxaemia. Each of these percentages is now divided in the proportion of the correct and incorrect forecasts by the Flicker Test for both toxaemia and non-toxaemia, which gives the following percentages:

Population

Toxaemia	11·4 per cent	Test+	7·66 per cent
		Test−	3·53 per cent
Non-toxaemia	88·6 per cent	Test+	32·43 per cent
		Test−	56·17 per cent

The probability of toxaemia being the true cause of a positive test outcome is then given according to a theorem of probability (Bayes' Theorem) by the ratio: percentage of correct diagnosis divided by the sum of percentages for correct and incorrect diagnoses. Applying this rule we obtain the following probabilities that a positive test outcome is really the effect of the presence of toxaemia and a negative outcome the effect of the absence of toxaemia.

Specificity of positive reaction $\frac{7 \cdot 66}{40 \cdot 09} = 19$ per cent

Reliability of negative reaction $\frac{56 \cdot 17}{59 \cdot 70} = 94 \cdot 1$ per cent

Applying now the same method to the Weight Test results, we tabulate the data of column 3, Table I (last block) as follows:

Weight Gain		*Sample*	
Toxaemia	Test+	36	90 per cent
	Test−	4	10 per cent
Non-toxaemia	Test+	5	22·7 per cent
	Test−	17	77·3 per cent

In order to see these sample results against the background of incidence in the population, we proceed as before, dividing the incidence rate 11·4 per cent according to the first two percentages of the above table, and the non-incidence rate of 88·6 per cent according to the second pair of percentages. This gives the following table.

Population

Toxaemia	11·4 per cent	Test+	10·30 per cent
		Test−	1·14 per cent
Non-toxaemia	88·6 per cent	Test+	20·1 per cent
		Test−	79·9 per cent

Applying Bayes' Theorem as before we obtain the following probabilities for a positive test outcome having as its true cause the presence of toxaemia and for a negative test outcome having for its cause the absence of toxaemia.

Specificity of positive reaction $\frac{10 \cdot 3}{30 \cdot 4} = 33 \cdot 8$ per cent

Reliability of negative reaction $\frac{79 \cdot 9}{81 \cdot 04} = 98 \cdot 2$ per cent

Comparing now the specificity figures for the Flicker and the Weight test, we cannot avoid the conclusion that the positive Weight test is a

safer indication of the presence of toxaemia than the positive Flicker test. The same, although to a much lesser degree, would seem to apply to the negative test, although the difference between 94 per cent and 98·2 per cent could hardly be regarded as important.

This method was used in the Paul Ehrlich-Institute at Frankfurt a.M for ascertaining specificity of the serum diagnosis of tuberculosis by means of the Haemagglutination Method after Middlebrook and Dubos (1948) and for ascertaining the specificity of the Wassermann reaction in syphilis.

Sample from Hospital Records

To discover if the weight-gain results truly reflected the overall situation a sample consisting of the records of all patients who had attended the appropriate clinics on or before 20 weeks of pregnancy up to or beyond 30 weeks during the first 5 months of the year was drawn from the Medical Records Department of Southmead Hospital. Of the 165 cases which emerged 66 were primigravidae. The figures were as follows:

Correct positive forecasts	32	
Correct negative forecasts	10	
Total correct	42	= 64 per cent
Incorrect positive forecasts	18	
Incorrect negative forecasts	6	
Total incorrect	24	= 36 per cent

These results, patently of the same order as those of the series, are surprising in that they too reveal an overwhelming bias in favour of toxaemia imposed on both groups by the definition used (considering the preponderance of positive tests), and on the studied group by the Weight-Gain Clinic population.

Any objection to the validity of conclusions drawn from these figures on grounds of their unrepresentative nature would be over-ruled if, in the normal population, the ratio of correct (negative) to incorrect (positive) forecasts were perpetuated—namely 5 to 17 (1 : 3) in the series proper, 10 to 18 (1 : 2) in the sample from records, giving an aggregate of 15 to 35, again 1 : 2.

Very much to the point is the statement of Nelson (1955) in his comprehensive study involving 1,457 cases which included 342 toxaemias that, "About two-thirds of the normal pregnancy group . . . came into the 8 pounds or over category". In the terminology of the present study this represents a ratio of correct negative to incorrect positive forecasts of 1 : 2.

It will be of interest to see whether the more extensive survey of this question at present in progress at Bristol confirms this ratio.

Effect of Acetazoleamide

A therapeutic trial of acetazoleamide (Schnieden, 1955), a sulphonamide apparently capable of increasing sodium excretion through inhibition of carbonic anhydrase in the kidney tubules, was made in 18 cases in this series 16 of which appear in the Weight-Gain Group.

Taking as his criteria of toxaemia visible oedema of both legs and hands, or a diastolic pressure above 99 mm. Hg, or albuminuria, Schnieden concluded that acetazoleamide, in conjunction with low sodium intake, did significantly lower the incidence of these signs. The reduction in the mean weekly gain in all groups treated with acetazoleamide, however, was not significant.

Table VI reveals that in this study too, there was no substantial difference between the mean weekly gain of the cases receiving acetazoleamide and that of all cases; but it should be noted that 10 out of the 16 developed pre-eclampsia.

Table VI

	Average Gain Ounces Per Week Acetazoleamide Cases	Average Gain Ounces Per Week All Cases
Correct positive forecasts (9 cases)	21·2	19·9
Incorrect positive forecasts (6 cases)	17·8	19
Incorrect negative forecasts (1 case)	7	7

Acetazoleamide, therefore, did not appear to exert any adverse influence upon the prediction of toxaemia in this instance.

Discussion

Brill and his co-workers consider the N.F.F.T. of great value in the prognostication of pregnancy toxaemia, and even find it a measure of the efficacy of treatment, and a means of differentiating cardiovascular or renal disease, "pseudo-toxaemia", and toxaemia. Marty and Hardy, in close agreement, affirm that the flicker test "cannot be denied a place in diagnostic methods", but they urge further study.

On the other hand we find that, although the N.F.F.T. test is correct in predicting the onset or absence of toxaemia in two-thirds of our group of cases, it exhibits an insufficient degree of specificity. This conclusion is in accord with that of Morris and his co-workers whose results appear to be more at variance with Brill's than do the present figures; but the high proportion of positive tests in their normal pregnancy group may arise from the (presumed) high proportion of single tests in that group (judged from the overall ratio of repeated tests and the fact that their normotensive patients were at term). Marty and Hardy stress the importance of repeated testing, their average being 4·2 examinations per patient; and we have found that the pattern of a positive first test followed by two or three negative tests is not unusual in non-toxaemic pregnancies.

Many writers challenge the theorems on which the tests rest that retinal vasospasm is a constant concomitant of early toxaemia and that the alteration in F.F.T. is due solely to the vasodilator action of nitroglycerine. Rogart (1953) could distinguish no correlation between F.F.T. response to nitroglycerine and fundal vascular change as seen on retinoscopy.

Gillim concluded that careful clinical assessment was just as good as the N.F.F.T. test in the detection of impending toxaemia.

While concurring with Nelson that the risk of pre-eclamptic toxaemia is greater among those primigravidae who have gained excessively, we do not think it is as great as that suggested by Hamlin. Nor can we substantiate his statement that the vast majority of "weight-sign-negative" patients do not develop toxaemia.

We find that, despite its predictions being correct in about 60 per cent of our cases, the weight sign is relatively unspecific as a test for the early detection of pre-eclampsia.

It is, however, appreciably more specific than the N.F.F.T. test; and is more practicable since it consumes less time, occupies less space, requires fewer special conditions, and has no side effects. In addition weight-recording is already one of the routine procedures at antenatal clinics all over the country.

To perform flicker tests, as described, on all antenatal patients would entail extra expenditure at a minimum rate of three of these costly flicker meters per clinic.

A final comment on the practical application of the weight-gain sign, at least in Bristol, must await the findings of the study in progress on the effects of diet control on the incidence severity, and outcome of toxaemia.

Summary

(1) Ninety-four pregnant women have had a varying number of Nitroglycerine Flicker-Fusion Threshold tests performed before delivery or the onset of pre-eclampsia as the case may be.

(2) Sixty-two primigravidae (55 of whom are included in the "flicker cases") were studied with regard to their weight-gain between 20 and 30 weeks gestation.

(3) An analysis of a sample from hospital records of comparable primigravidae was in close agreement with the results from the weight-gain group above.

(4) Because of their relative lack of specificity on statistical appraisal, we attach less importance to the Nitroglycerine Flicker-Fusion Threshold test and to the weight-gain sign as prognostic measures in pre-eclamptic toxaemia than do Brill *et al.* and Hamlin. However, our estimate in this respect depends upon the general validity of the assessed incidence of toxaemia in the population (11·4 per cent).

(5) The weight-gain sign, although equally sensitive, is the more specific and practicable of the two tests.

(6) The effect of acetazoleamide, administered

to some of the patients in this series, was found to be negligible.

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MESODERMAL MIXED TUMOUR OF THE UTERUS

Case Report and Review of the Literature

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MESODERMAL mixed tumour of the uterus is a rare condition; the first case was probably reported by Wagner in 1854, when he described the tumour as an enchondroma of the uterus. Weber (1867) first described the condition in the cervix, whilst three years later Anderson-Erdmannson (1870) first recorded a case of the tumour arising from the body of the uterus.

Since this time, isolated cases and small series have been reported initially from Germany, and more recently from the United States of America. Few cases have been recorded in Britain; Glynn and Blair-Bell (1914), Nicholson (1918), Murray and Littler (1914), Shaw (1928), Hartfall (1931), Lochrane (1933), Meikle (1936), Willis (1948), Blumer and Edwards (1948) and Ferreira (1951) have all described cases and discussed the literature.

Because the condition is such a rarity, it is important that all cases should be recorded, for only in this way will knowledge of the incidence, clinical features, pathology and treatment be enhanced.

CASE REPORT

Mrs. A.V., aged 72 years, was seen for the first time in the Gynaecological Department in July, 1956, complaining of post-menopausal bleeding. The bleeding had started two weeks previously as a small "show", which had lasted two or three days and then ceased. One week later, the bleeding restarted and had continued, the loss becoming increasingly heavy until it was now heavier than a normal period.

The patient had had 2 miscarriages and 10 normal confinements before the menopause occurred at the early age of 42 years; she gave no history of past illnesses. The general condition of the patient was good for a woman of her age, though she was noted to be obese.

Abdominal examination revealed the presence of a large, firm, ill-defined swelling of limited mobility, extending from the left costal margin across the midline and almost down to the level of the umbilicus. The surface of the mass was regular, and the abdomen was resonant all over the swelling.

On pelvic examination, the cervix was seen to be healthy, there was present a mild degree of senile vaginitis, and the uterus was bulky, anteverted and of limited mobility.

Investigations

A cervical smear revealed no evidence of malignant cells. At this stage, the abdominal mass was considered to be either arising from the stomach, or possibly to be a mass of neoplastic glands. X-ray examination of the stomach showed that the mass was probably adherent to the lesser curvature, but not extending into the lumen of the stomach. The radiologist was of the opinion that the swelling was a large peritoneal metastasis. Chest X-ray showed no evidence of neoplasm. A histamine test meal was normal and a glucose tolerance test showed a typical diabetic curve.

Examination under anaesthesia confirmed that the cervix was healthy and that the uterus was anteverted, bulky, and tethered anteriorly. A mass of necrotic, friable material was removed from the uterus; this was thought to be carcinoma of the corpus. Seventy milligrams of radium were inserted into the uterine cavity, and 20 milligrams were placed in each lateral fornix. This remained in the patient for twenty-four hours.

Biopsy Report

"Section shows a pleomorphic sarcoma with many mitoses. Many giant and bizarre cell forms are present. In addition there are numerous cells with abundant eosinophilic cytoplasm and in some of these cross striations are present. The histological appearance is that of a mesodermal mixed tumour of the uterus."

In view of the highly malignant nature of the growth, and the presence of the large abdominal mass, presumably secondary growth, a course of deep X-ray therapy was started. It was hoped that the X-ray therapy would possibly reduce the size of the mass, and increase the chances of success of any subsequent operation.

1,600 r was given to four abdominal fields for seventeen days. No further vaginal bleeding occurred after a few treatments with deep X-rays; however, the patient became increasingly nauseated, and the abdominal mass appeared to be unchanged. After two weeks of deep X-ray therapy, the patient began to vomit. On the seventeenth day, the treatments were discontinued. By now, the patient was extremely ill and the vomiting had become almost incessant, at times containing altered blood. The patient died two days later.

Summary of Post-mortem Report

The only abnormal findings were in the abdomen. The left ovary was replaced by a partly solid and partly cystic tumour, 4 cm. in diameter, which was infiltrating the adjacent Fallopian tube and sigmoid colon; the mucosa of the colon was not involved. The right ovary was normal. There was widespread and massive involvement of the peritoneum by metastatic growth, much of which was haemorrhagic and necrotic, and the peritoneal cavity contained two litres of blood-stained fluid. One large mass of growth in the greater omentum was attached to and invading the anterior abdominal wall.

The uterus, which was 8 cm. long, was firmly attached to the bladder by metastatic growth and nodules of growth were scattered over the serosal surface; infiltration of the myometrium by these growths was minimal. The uterine cavity was filled by a pedunculated tumour, much of which was haemorrhagic and necrotic. It measured $4 \times 2 \times 2$ cm. and arose from the fundus on the anterior wall. Around the pedicle, the tumour extended for 1 cm. as a firm white thickening of the endometrium with only superficial infiltration of the myometrium.

Histology

Sections of the ovarian tumour showed a well differentiated papillary adenocarcinoma with numerous "psammoma" bodies. The peritoneal growths showed a similar structure.

Sections of the uterus showed the endometrial tumour to be a mesodermal mixed tumour. Apart from more necrosis, the histological appearance closely resembled the biopsy material. There was only superficial infiltration of the myometrium. At the edge of the tumour occasional endometrial glands could be seen but there was no epithelial component in the tumour itself.

The growth on the serosal surface of the uterus was a well differentiated adenocarcinoma which invaded the myometrium for only a very short distance. There was no continuity between this growth and the endometrial tumour.

Comment

The post-mortem findings showed that there were two distinct tumours; firstly a carcinoma of the ovary with widespread peritoneal dissemination, and secondly a mesodermal mixed tumour of the uterus with no metastases.

Nomenclature

Most cases are now called mesodermal mixed tumours, a term first used by Kehrer as long ago as 1906. MacFarland in 1935 discovered more than one hundred names to describe the condition, and some cases are still reported under other names, usually descriptive of some particular constituent of the tumour, rhabdomyosarcoma, chondrosarcoma, myxosarcoma, etc. Besides the "cell type" terminology, the early German writers coined many highly descriptive terms; "Traubige myosarcoma striocellulare" Pernice (1888), "Sarcoma colli uteri hydropicum papillare" Spielgelberg (1879), and "Myxoma enchondromatodes arborescens colli uteri" referred to by Rein in 1880. In more recent times, McFarland (1935) has advocated the term dysontogenetic tumour; Stout (1948)

used the name mesenchymomata; whilst Hill and Miller (1951) have re-introduced the broader description carcino-sarcoma. However, mesodermal mixed tumour seems to be the most useful and widely recognized name, although it hardly describes the high degree of malignancy of the tumour. While some measure of agreement seems to have been reached regarding the nomenclature of the tumours, the pathology remains very undecided.

Pathology

Mesodermal mixed tumours may arise from the cervix or body of the uterus. In contrast to carcinomata the tumours are found more often arising from the corpus. Cervical tumours develop from a narrow pedicle, giving rise to grapelike vesicles. The growth can reach a large size, filling the vagina and even protruding through the vulva.

Corporeal tumours may grow from any part of the uterine cavity, more usually from the fundus, arising from a broad pedicle. These growths are said to be firmer than the cervical growths and may reach the size of an adult head.

A moderate sized corporeal growth may be extruded through the cervix and give the appearance of a pedunculated fibroid such as was described by Lochrane (1933) or softer placental tissue described by Hardy and Moragues (1952). Most authors comment upon the vascularity of the tumours, and relate this to the extreme malignancy.

A mesodermal tumour is composed of a variety of mesodermal constituents. Willis (1948) describes cellular sarcomatous tissue, cartilage or embryonic pre-cartilage, adipose tissue, striated muscle fibres or eosinophilic cells, and mentions that various other tissues are often combined in these tumours.

Epithelial elements are not usually considered to be part of the actual tumour. However, Willis (1948) takes the view that the abundance of endometrial or cervical tissue in some tumours at least shows great concomitant hyperplasia if not metaplasia.

Wilson *et al.* (1953) agree with this view which is supported by the discovery in certain tumours of epithelium which has undergone carcinomatous change; such cases have been reported by Penkert (1905), Schröder and Hillejahn (1920), Nicholson (1918), Thiery and Brunschwig (1955), Hill and Miller (1951) and Ehrlich (1942).

The presence in the tumour of two or more heterotopic constituents is considered by many authors to be essential for the tumour to be designated "mesodermal mixed tumour" (Shaw, 1928; McFarland, 1935; Thiery and Brunschwig, 1955).

Whilst in agreement with this, Läwen (1905) considered that in addition there should be present embryonic striated muscle fibres before the tumour could be classified as mesodermal mixed tumour. This view is supported by Ehrlich and Lebowich (1941).

This extremely limited viewpoint is not accepted by many authorities at the present time, for, as Meikle (1936) pointed out, only very early embryonic muscle fibres may be present in which transverse striations are not fully developed.

Hardy and Moragues (1952) are of the opinion that it is unreasonable to exclude a tumour which is made up of heterotopic elements and which follows the characteristic course of the condition, because striated muscle cells cannot be demonstrated. Many authors have commented upon the difficulty in demonstrating these embryonic cells; Willis states that half the cases show these cells and many more would possibly show striations if more thorough examinations were carried out.

Glynn and Blair-Bell (1914) and Shapiro (1931) have noted cells with vesicular nuclei, often multiple, placed within deeply eosinophilic, finely granular, vacuolated cytoplasm; and considered these cells to be indicative of mesodermal mixed tumour.

A loose myxomatous connective tissue has been noted on many occasions, which was thought to be embryonic mesenchymal tissue by Wilms (1899), Shaw (1928), Nicholson (1918) and Seydel (1901).

Amolsch (1939) maintained that the presence of this loose myxomatous connective tissue was definite evidence of an embryonic constituent, and believed this to be strong evidence of a mixed malignant tumour.

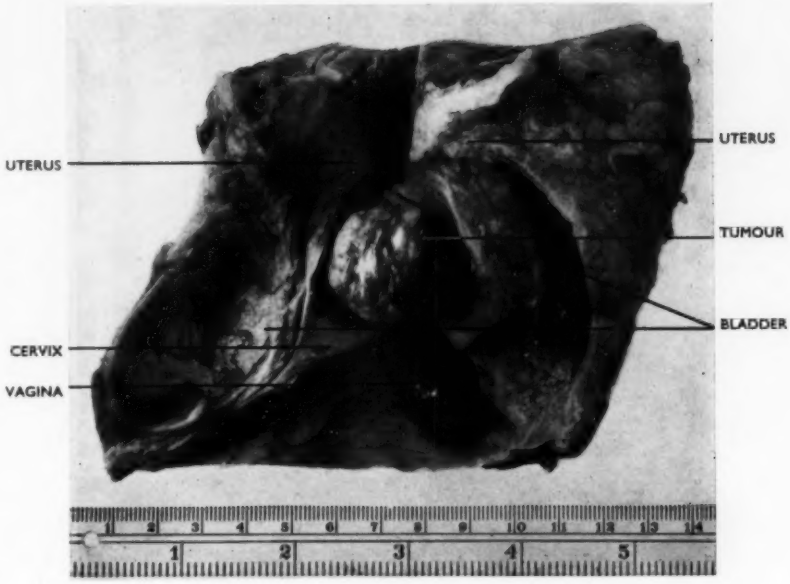

FIG. 1

Photograph of the bladder, uterus, cervix and vagina opened anteriorly, showing the pedunculated mesodermal mixed tumour and the secondary deposits of adenocarcinoma invading the bladder and uterus.

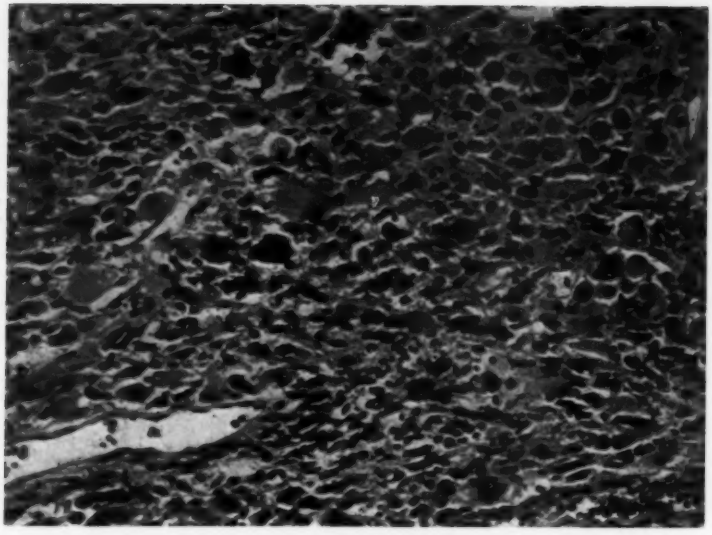

FIG. 2

Representative area of biopsy material showing a pleomorphic sarcoma. Haematoxylin and eosin. ×200.

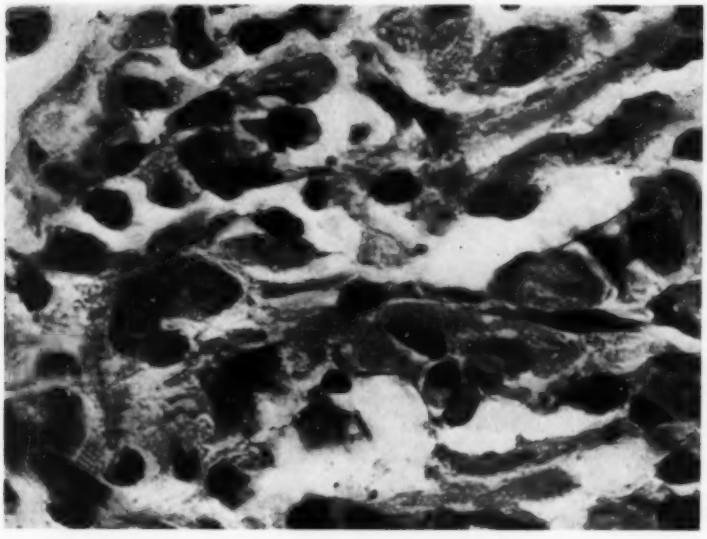

FIG. 3

Higher power to show striations. Haematoxylin and eosin. ×850.

The sarcomatous stroma may consist of round cells, spindle cells, or giant cells. Glass and Goldsmith (1941), in a review of cases reported prior to 1941, found that the stroma contained spindle cells in 94·8 per cent, round cells in 37·9 per cent and in 32·8 per cent of cases giant cells. Stromal cells, however, are of little value in any classification because a mixture of cells is often present. Cartilage was found in the first case reported, and Meikle (1936) discovered that it was present in 28 out of 45 tumours of the corpus, and 20 out of 31 tumours of the cervix; Willis (1948) mentions that cartilage or embryonic pre-cartilage is present in three-quarters of the tumours.

The answer to the problem of the pathology will probably lie somewhere between the view that only tumours exhibiting striated muscle should be considered as mesodermal mixed tumours; or some combination of two or more heterotopic elements with myxomatous connective tissue, and granular eosinophilic cells.

If the rigid criterion laid down by Läwen (1905) is not accepted, all manner of other sarcomata may well be indiscriminately labelled mesodermal mixed tumour, and until pathologists can agree upon the criteria necessary for a tumour to be included in this group, the true incidence of the condition will not be known.

Histogenesis

Hartfall (1931) commented that the histogenesis was of great complexity; this is still true twenty-five years later, for the problem remains unsolved.

Hypotheses to account for these tumours are elaborations upon two basic considerations. One postulates that by a process of metaplasia all the heterogeneous tissues are derived from the connective tissues of the uterine mucosa. The other is based upon Cohnheim's hypothesis of cell rests; Pfannenstiel (1892), Nicholson (1918), Willis (1948) and others have supported the first view in broad outline, whilst Wilms (1899), Meikle (1936), Kehrer (1906), Glass and Goldsmith (1941), and others have written in favour of the latter. Excellent arguments have been put forward in favour of these hypotheses, but a difficulty common to both is why and how cells can remain dormant in a uterus which is ever changing with menstruation and pregnancies, and yet may suddenly be stimulated to grow into highly malignant tumours.

Hormonal disturbance has been proposed as a possible factor initiating the neoplasia, but at the present time there is no evidence to support this suggestion.

Previous Irradiation

The occurrence of subsequent malignancy has stimulated many writers to condemn the use of X-ray or radium sterilization in the treatment of excessive bleeding (Corscaden, 1948; Schmitz and Towne, 1947; Smith and Bowden, 1948; Speert and Peightal, 1949; Thornton *et al.*, 1951; McFadyen, 1952). It is perhaps more than a coincidence that so many cases of mesodermal mixed tumour have arisen in patients who have previously been irradiated for benign conditions. Hill and Miller (1951) have suggested this as an aetiological factor; Joffe, Eckman and Wells (1948), McElin and Davis (1952), Kight (1953), Klein (1953), Wilson *et al.* (1953), Schiffer, Mackles and Wolfe (1955) and Brennan (1956) have all reported such cases.

Symptoms, Signs and Diagnosis

Post-menopausal bleeding, or a foul vaginal discharge are the presenting symptoms in almost every case. Pelvic pain and urinary symptoms are occasionally encountered in late cases. An abdominal swelling or a polypoid tumour protruding through the cervix may be found in the more advanced cases. The diagnosis can only be made on histological evidence.

Prognosis

The outcome is usually fatal within 6 to 12 months. It is rare to find a patient who has survived more than 24 months. Instances have been reported of patients surviving longer, but in these cases the diagnosis must be suspect.

Treatment

The results of radical surgery, irradiation, or a combination of the two appear to give uniformly bad results. Early diagnosis, were this possible, might alter the outcome a little, but the paucity of symptoms especially the lack of pain tends to make patients procrastinate and seek medical

advice too late. In any case, it would seem that the growth develops so rapidly that curative treatment is not possible.

The tumour being embryonal in nature it may be expected to be highly radiosensitive, but this unfortunately is not the case.

Discussion

This case presented in the typical manner; post-menopausal bleeding occurring in an obese woman, later shown to be a diabetic. Obesity has been noted in many cases, but only Thiery and Brunschwig (1955) have reported the condition arising in a diabetic patient. Way (1954) suggested that there is an increased incidence of carcinoma of the corpus uteri in the diabetic subject. This also may be found to apply to mesodermal mixed tumour when sufficient cases are discovered.

The histology confirmed without any doubt the presence of "double pathology" in this case. Thiery and Brunschwig (1955) similarly found carcinoma of the sigmoid colon in one of their cases.

Bickle and Bennett (1954) have suggested that the condition is probably not as rare as has been thought in the past. Douglas (1953) mentions a large number of cases occurring recently in various American hospitals, but few new cases have been reported in the intervening 4 years.

Summary

(1) A case of mesodermal mixed tumour of the uterus is described.

(2) The apparent rarity of the condition in Britain is commented upon.

(3) Reference is made to the nomenclature of the tumour.

(4) The pathological characteristics are discussed.

(5) A brief mention is made of two main theories of histogenesis.

(6) Comment is made upon the possibility of previous irradiation as an aetiological factor.

(7) The diagnosis can only be made by histological examination.

I wish to express my thanks to Mr. J. H. Peel for kindly permitting me to publish details of this case, and to Dr. B. S. Cardell of the Department of Pathology for his most valuable assistance.

I would also like to thank Mr. G. Harwood and Mr. W. Smith for the photomicrographs and the photograph.

Addendum

Since this paper was prepared, a further case has been reported by Korn, G. W. (1956).

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ON THE TRANSFER OF BARBITURATES TO THE HUMAN FOETUS AND THEIR ACCUMULATION IN SOME OF ITS VITAL ORGANS

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IT has been known for quite a long time that many drugs given to the mother pass the placenta and appear in the foetus. Thus Dille (1934, 1936) observed that certain derivatives of barbituric acid even when administered in small doses could be detected in the foetal blood of different animals. These observations have been confirmed by other workers in various animal experiments.

The fate of the barbiturates in the foetal body, i.e., their accumulation and metabolism, seem, however, to be practically unknown. Nor do any reliable facts seem to be known about the possible pharmacological effects on the foetus or the newborn baby (cf. Martland and Martland, 1950; Weyers, 1952; Kahn, Nicholson and Assali, 1953).

These circumstances are remarkable considering the widespread and sometimes indiscriminate use of high doses of sedatives containing barbituric acid in pregnant women, especially in toxaemia. It therefore seems an urgent task to throw some light upon this apparently neglected problem in obstetrics. The present investigation was undertaken in order to determine in what amounts and how quickly some common barbiturates pass over to the human foetus when given in ordinary doses to the mother. The quantitative distribution within certain vital organs of the foetus has also been investigated. This experimental work seems to be a sound basis for further studies concerning possible effects on the foetus.

MATERIAL

A total of 35 human foetuses have been analyzed after legal abortions at the 4th to the 7th lunar month of pregnancy. At the operations samples were taken of the mothers' venous blood and urine whilst the foetal material taken for analysis included cord blood, placenta, liver, and brain. From the brain specimens of the cortex as well as of a region including the fourth ventricle with its bordering tissue were cut out for analysis. In certain cases the amniotic fluid as well as the foetal kidneys, adrenals, meconium, and urine were analyzed.

METHODS

Administration of Drugs

The drugs used were Amylobarbitone (Isomylnatrium Hässle-Tika), Phenobarbitone (Fenemalnatrium ACO) and Barbitone (Diemal ACO). The doses given were Amylobarbitone 0·25 g. intramuscularly, Phenobarbitone 0·20–0·25 g. intramuscularly, and Barbitone 0·50 g. orally. The time interval between drug administration and operation varied between 30 minutes and 50 hours.

Operative Technique

Vaginal or abdominal hysterotomy was used throughout the series. The anaesthesia used was N_2O-O_2-ether in a closed system. All the operations were performed by one or other of the authors thus facilitating an immediate and uniform method of collecting the material for analysis. Care was taken to avoid damaging the foetal tissues.

Principles of Method

The ultraviolet spectrophotometric method described by Goldbaum (1952) is based on the change in the absorption spectra of barbiturates at pH 14 and 10·5 respectively. He has found that the difference in optical density measured at these two hydrogen ion concentrations at 260 mμ is specifically related to the barbiturate concentration. A barbituric acid derivative (except the n-methyl and thio derivatives) is indicated when a maximum positive difference appears at 260 mμ and a maximum negative difference at 240 mμ. The optical density at 305 mμ indicates the amount of absorbing substances other than barbiturates. According to Goldbaum barbiturate concentrations of 0·1 mg. per 100 ml. of blood and 0·3 mg. per 100 g. of tissue can be determined with a high degree of accuracy.

The method used in this investigation principally follows that of Goldbaum. When testing the different phases of the procedure some modifications have been adapted. Hereby a better reproducibility and a higher sensitivity of the method were attained (*vide infra*).

Procedure

For details the reader is referred to Goldbaum (1952). The procedure implies the following steps. The specimens are extracted with chloroform which is then filtered and extracted with sodium hydroxide. The alkaline solution is centrifuged and transferred to quartz cuvettes. The optical density readings are made at 305, 260, and 240 mμ in a Beckman DU spectrophotometer. Distilled water is put through the procedure and its alkaline extract is used as the reference solution. All determinations were made in duplicate.

Discussion of the Method

In his paper Goldbaum recommends the use of ethylene dichloride instead of chloroform for the extraction of brain tissue. In our hands, however, the chloroform extraction of this tissue gave the best results (cf. also Broughton, 1956). When extracting the specimens we constantly used 15 volumes of freshly distilled and washed chloroform. The homogenization of the tissues seemed to be of special significance for the barbiturate recovery. By using a high speed stainless steel homogenizer (40,000 r.p.m.) the recoveries were quite reproducible from different parts of a single tissue specimen, e.g., the liver. Firstly using ordinary pear-shaped separating funnels we found the results of the double tests to be less accurate. By changing to specially made cylindrical glass funnels and by using a shaking apparatus permitting a standardized extraction procedure the test results became highly reproducible. An extraction time of 3 minutes proved to be optimal for all specimens tested.

As mentioned above Goldbaum's method has a sensitivity allowing determination of 0·3 mg. barbiturate per 100 g. of tissue. When using the modifications just outlined the sensitivity of the method became twice as high. In a series of determinations of Amylobarbitone solutions we found the recovery to be practically complete up to a concentration of 1 mg. per 100 ml. (Fig. 1).

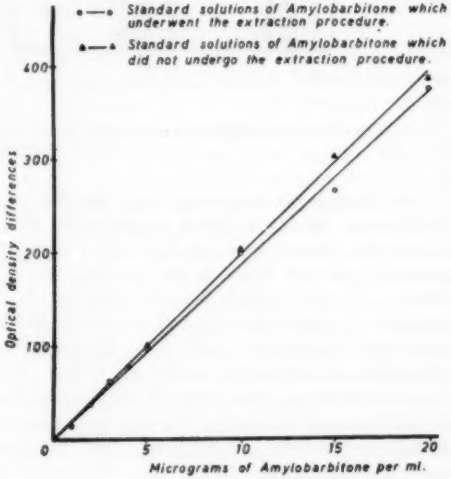

FIG. 1

Barbiturate recovery after the extraction procedure.

For practical reasons some of the samples were stored in a deep freeze at −30° C. until taken for analysis. Such storage for as long as one week produced no significant changes as shown by several control determinations.

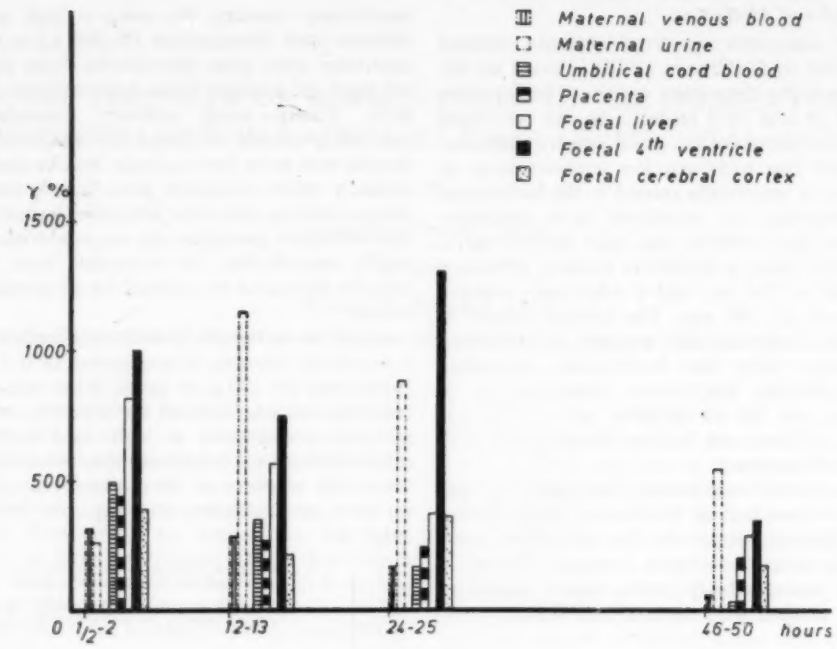

FIG. 2

Barbiturate concentrations in maternal and foetal material during the first 2 days after injection of 0·25 g. of Amylobarbitone to the mothers.

The drug levels occurring after the doses of barbiturate given in these experiments differ in various organs between 0·5 and 17 microgrammes per ml. fluid or per g. solid. Within this range the optical density readings show extinction values from 0·010 to about 0·300 with the instrument used. The blanks never exceeded an extinction value of 0·004. The small variations in the optical density differences at 260 mμ, which might be due to naturally occurring absorbing substances, will produce an error of less than 10 per cent. This error is most obvious in urine but can be significantly reduced by thorough washing with phosphate buffer. Concerning blood and other tissues, however, we found that nothing was gained by such a washing. This observation is in contradiction to the data given by Broughton (1956).

Metabolites of barbiturates in which the ring structure remains intact have ultraviolet spectra similar to those of the original compounds (Maynert and Dawson, 1952; Lous, 1954; Raventós, 1954). Thus such metabolites might interfere with the determination of the unchanged drug. According to Broughton (1956), however, it is highly probable that the metabolites will be hydrolyzed in alkali at a rate different from that of the original barbiturates. In his investigation Broughton found that the influence of these metabolites is not sufficient to interfere with Goldbaum's method.

As pointed out by Lous (1950), Goldbaum (1952), Nielsen and Praetorius (1952), Dybing (1955), Askevold and Løken (1956) and Broughton (1956), sulphonamides and related compounds as well as salicylic acid may produce quantitative errors in barbiturate estimation. Therefore in the present investigation care was taken that no such drugs were given to the patients within 3 days of the operation. On the

other hand pre-operative medication with morphine and scopolamine or promethazine did not noticeably influence the optical density of the various extracts as was shown in control determinations. Nor did quinine have any effect in this respect.

Results

The amounts of barbiturate found in the various samples after different time intervals are graphically outlined in Figure 2. The columns represent mean values of Amylobarbitone given to 20 cases. Tissue and liquid sample determinations not found in Figure 2 as well as Phenobarbitone and Barbitone material are presented below.

Already within 2 hours the Amylobarbitone concentration has reached its maximum level in most of the foetal samples. In the maternal urine, however, this level is reached after about 12 hours and then gradually diminishes without completely disappearing during the time of observation. The rate of disappearance of barbiturate is similar in foetal and maternal blood, and in both has practically disappeared in 2 days.

There is an accumulation of barbiturate in the foetal liver most obvious at 48 hours. At this time even placental tissue seems to retain a certain quantity of barbiturates.

Of special interest in this investigation is the strong accumulation of barbiturate within the region of the 4th ventricle. The concentration here is more than twice as high as in the cerebral cortex during the first day after administration. Even after 48 hours it still remains at a comparatively high level.

In 10 cases 0·20–0·25 g. of Phenobarbitone was administered intramuscularly to the patients. The drug levels in the maternal blood and urine as well as in the umbilical cord blood were very much the same as for Amylobarbitone. In the placenta, foetal liver, and brain the amount of barbiturate was even higher than that found with Amylobarbitone, in some cases up to twice as much. It is interesting to note that a similar trend of accumulation was found when 0·50 g. Barbitone was given by mouth 12–14 hours before operation (5 cases).

The concentration of Amylobarbitone in the amniotic fluid during the first day after injection varied between 100 and 200 γ per cent (7 cases). During this time the drug level in the meconium, tested in some few cases, was above 1,000 γ per cent. These cases were also tested for barbiturate accumulation in the foetal kidneys and adrenals. This was found to be within a range of 1,000 to 1,500 γ per cent, the higher values being found in the adrenals. In 3 cases the foetal urine contained no barbiturate at all after 12, 24, and 48 hours, respectively.

Discussion

As pointed out by Kahn *et al.* (1953) there are certain factors to consider when discussing the possible effects of barbiturates on the foetus: (1) the susceptibility of the foetus to the drug, (2) the amounts received by the foetus, and (3) the duration of their accumulation. The present investigation does not permit any conclusions to be drawn about the first factor. Obviously this problem can hardly be studied on human foetuses but might lend itself to controlled observations on newborn infants.

Concerning the other factors mentioned the experiments presented in this paper have given clear-cut results about the transmission of the drugs used across the placenta, the accumulation within some vital foetal organs, and the approximate rate of elimination of the drug by the mother and the foetus. There are several reports on these problems but the diversity of the results is profound due to widely varying experimental conditions and to less accurate methods of analysis. Moreover, the data found in the literature are based on animal experiments. As far as we know, there have been no previous reports published on quantitative determinations of barbiturates in human foetuses.

Fabre (1933) in dogs, Dille (1934, 1936) in rabbits, cats and guinea pigs as well as Windle and Becker (1941) in cats and guinea pigs found quite a rapid transfer of various barbituric acid derivatives through the placenta to the foetus. These observations have been confirmed in determinations on parturient women (Dreisbach and Snyder, 1943; Hellman *et al.*, 1944; Kahn *et al.*, 1953; Crawford, 1956). These results on human material were reached, however, by using thiobarbiturates, which have

certain metabolic properties making them incomparable with other barbiturates. In our investigation we have found a quick transference of Amylobarbitone from the maternal to the foetal side of the placental barrier. In a few cases examined, in order to determine the rate of the placental transmission, Amylobarbitone was found in comparable quantities in foetal and maternal blood within the first 30 minutes after an intramuscular injection of the drug into the mother. In no experiments have we been able to find any signs of delay in transference of barbiturates in the placenta. It seems, however, as though some kind of storage of the drug is taking place in the placental tissue, as is evident at the 48-hours interval (Fig. 2).

The essential role played by the liver in the processes of degradation of barbiturates has been pointed out by several authors (Masson and Beland, 1945; Kelly and Shideman, 1949). The former classify the various barbiturates according to their site of detoxification. Amylobarbitone belongs to the group mainly detoxified by the liver whereas Phenobarbitone is partly inactivated and eliminated by the kidneys. In his review Raventós has pointed out that practically 100 per cent of administered Barbitone is excreted unchanged in the urine of adults. Thus the above mentioned possible interactions of ultraviolet absorbing metabolites in our barbiturate determinations might be ruled out because of the general parallelism between the Barbitone and Amylobarbitone concentrations measured.

As seen in Figure 2 the concentration of Amylobarbitone in the foetal livers is rather high already ½–2 hours after injection and decreases very slowly during the time of observation. This accumulation might indicate an exhaustion of the detoxicating capacity of the foetal liver. It should be emphasized, however, that the present work does not permit any conclusions to be drawn about the mechanism of detoxication or elimination of the barbiturates found in the foetus.

So far as our few determinations of barbiturates in the foetal urine (gained by puncturing the bladder) may be taken as representative for the material as a whole, it seems as if the elimination of the drugs did not occur by the action of the kidneys. The disagreement between the concentration in the kidneys and in the urine mentioned above might be due to a high detoxifying ability of the kidneys or, more likely, to an inability of the foetal kidneys to eliminate the barbiturate. In this connexion it is worth while pointing out the low but relatively constant concentration of barbiturates in the amniotic fluid and the large amount found in the meconium.

The very high concentration of barbiturate found in the adrenals may in part be due to the solubility of the drug in lipids.

In our opinion the most interesting observation in the present series is the high amount of barbiturates found in the region of the 4th ventricle of the brain. The outstanding difference between the barbiturate concentration in the cerebral cortex and in the 4th ventricle area assumes importance in relation to the well-known respiratory depressant effect of barbiturates (cf. Hughes, Hill, Green and Davis, 1950; McCall and Taylor, 1952). This specific concentration of barbiturates in the region of the 4th ventricle has been reported in an investigation on rats by Goldschmidt, Lamprecht and Helmreich (1953). This phenomenon cannot possibly be due to a higher proportion of myelin in the brain stem than in the cerebral cortex at the actual stage of development of the foetus.

The relatively higher barbiturate concentrations within the ventricle region after the first and third intervals (Fig. 2) may hardly be explained by inaccuracies of the method due to the small amounts of tissue available to extraction. If so, the cerebral cortex which can be gained in large amounts would not show equivalent variations. The pharmacodynamic aspects of this finding are beyond the scope of this investigation.

Summary

By means of a modified ultraviolet spectrophotometric method the transfer of barbiturates from the maternal to the foetal organism was studied during the 4th to the 7th months of human pregnancy. The barbiturates used were Amylobarbitone, Phenobarbitone, and Barbitone. They were given in ordinary sedative doses to the mothers from half an hour up to 50 hours

before legal abortions were performed by hysterotomy. The maternal blood and urine were analyzed as well as samples of the foetal cord blood, placenta, liver, brain, and, in some cases, specimens of the amniotic fluid, the foetal kidneys, adrenals, meconium, and urine.

An approximate equilibrium between the maternal and foetal blood was reached during the first 30 minutes after an intramuscular injection of 0·25 g. of Amylobarbitone to the mother. The rate of the barbiturate elimination from the blood was about the same in mother and foetus.

An accumulation of barbiturate was found within the placenta and, more pronounced, in the liver and brain tissues.

In the brain the drug was found in a much higher concentration within the region of the 4th ventricle than in the cerebral cortex. Attention is called to the vicinity of the respiratory centre to the 4th ventricle.

Acknowledgments

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ANGULAR PREGNANCY

A Case Report with a Brief Review of the Literature

BY

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GESTATION occurring in the cornu of the uterus has been recognized at autopsy for 200 years. Grusetz and Polayes (1944) record that Traub was the first person to operate on such a case. In 1893 he performed a laparotomy for a suspected tubal pregnancy. Finding the gestation sac situated in the cornu of the uterus he performed a subtotal hysterectomy with subsequent recovery of the patient.

Confusion has arisen concerning the classification of pregnancies arising around the tubo-uterine junction. Various writers refer to interstitial pregnancy, angular pregnancy and cornual pregnancy as the same condition. It would be better if the term cornual pregnancy were confined to a gestation in the horn of an abnormal uterus.

Interstitial pregnancy implies implantation within the intramural portion of the Fallopian tube. Such a case has most commonly terminated by rupture of the gestation sac after 8 to 12 weeks though a few have developed to term. A search through the literature written in English reveals that 271 such cases have been recorded. There is no doubt that many of these were in fact angular pregnancies.

Munro Kerr and Anderson (1934) first drew attention to angular pregnancy. In this condition implantation has occurred in the extreme angle of the uterine cavity or at the innermost end of the interstitial portion of the Fallopian tube. Advancement of the pregnancy produces dilatation of the cornu with subsequent distortion of the uterus.

Undoubtedly this is a rare condition and only 14 proven cases and 6 doubtful ones are to be found. Munro Kerr and Anderson (1934) have seen 6 though they record only 2. Miles Phillips (1935) stated that he saw 4 cases. Riddell and Scholefield (1938) reported a case which terminated in rupture of the uterus at 32-weeks gestation. Saave (1953) treated a patient with an angular pregnancy following a salpingectomy for a previous tubal gestation. Rupture of the uterus occurred after 20 weeks. Wilson (1935), Gibberd (1936), and Dissick (1953), have each reported cases, though Wilson's case is doubtful.

Angular pregnancy is not as uncommon as it would appear. Many cases of so-called interstitial pregnancy have been, in fact, angular pregnancies. Gibberd (1936) believes that reports on gestation occurring in diverticula of the uterus have sometimes been mistaken for angular pregnancy.

The anatomical proof of the condition rests ultimately on the demonstration of the site of implantation of the ovum. Because this is not always possible, the criteria laid down by Munro Kerr and Anderson (1934) will establish the diagnosis. These are: (1) pain, (2) lateral distension of the uterus, (3) tendency to abortion with uterine haemorrhage.

These features are not present in every patient. In fact Gibberd's case and one case of Miles Phillips were not discovered until retention of the placenta occurred after spontaneous delivery.

It appears that angular pregnancy may terminate in the following ways:

(1) Rupture of the uterus with expulsion of the products of conception into the peritoneal cavity.

(2) Spontaneous abortion.

(3) Correction of the condition to a normal intra-uterine pregnancy. In this type the

placenta may be retained in the sacculation of the cornu, hysterectomy being necessary for its removal.

The case to be described falls into the first category, rupture of the cornu having occurred early in pregnancy with considerable intraperitoneal haemorrhage.

Case Report

A woman of 36 complained of 13-years primary infertility. Her general health was normal and her menses which appeared every 28 days persisted for 5 days. Her cycle was regular until 4th May, 1956, when menstruation occurred 3 days late and persisted for 14 days with a slight but continuous show daily. At this time a nagging ache commenced in the left iliac fossa. She was able to carry on with her normal household duties until 6 a.m. on 15th June, 1956, when a sudden explosive pain in the left lower abdomen associated with severe vaginal haemorrhage necessitated her going to bed and calling her doctor. The pain spread slowly over the lower abdomen and at 3 p.m. she complained of pain behind both shoulders. Increasing weakness was observed, the patient finally fainting at 5 p.m. just prior to her admission to hospital.

On examination she was extremely pale and shocked. The pulse of 130 per minute and blood pressure of 90/60 indicated considerable circulatory disturbance.

The abdomen was distended; there was withdrawal tenderness in all quadrants and extreme local tenderness in the left lower quadrant. The breasts were congested but no colostrum could be expressed from the nipples.

Vaginal examination revealed a hyperaemic vagina and cervix. Fresh bleeding appeared through the closed external os. The uterus, lying in the anteverted position, soft and bulky, was extremely tender. There was a distinct fullness in the left fornix and pouch of Douglas.

The provisional diagnosis was rupture of a left tubal gestation. A transfusion of compatible blood was commenced and arrangements were made for urgent laparotomy.

At 6.30 p.m. under an anaesthetic of Pentothal Sodium, Flaxedil and intratracheal nitrous-oxide and oxygen, the abdomen was opened through a right lower para-median incision with the patient in moderate Trendelenburg's position. A large amount of clotted and fresh blood was found in the peritoneal cavity. Both Fallopian tubes and ovaries were normal.

The uterus, slightly enlarged, was distorted by a dilatation in the region of the left cornu. It was perforated on its posterior wall, the orifice, 2 centimetres in diameter, lying 3 centimetres below and behind the left internal tubal meatus. A finger inserted through the perforation revealed a cavity, 5 centimetres in diameter. Both the uterine cavity and the internal meatus of the Fallopian tube communicated with this cavity. Diffuse haemorrhage occurred from the walls.

The distance between the uterine attachment of the round ligament and the tubal meatus was found to be the same on each side.

As much blood as possible having been aspirated from the peritoneal cavity, Bonney's myomectomy clamp was applied to the lower uterus and ring forceps clamped on each ovarian artery to reduce haemorrhage. The left cornu was then excised together with the adjacent portion of Fallopian tube, the outer end of the latter having been first ligated. The cavity was thus treated as a myomectomy and closed by a series of interrupted chromic catgut sutures, the peritoneal surfaces being approximated with plain catgut.

Once haemostasis was established, 2 pints of blood were administered rapidly while the abdomen was closed in layers without drainage.

An uneventful convalescence followed. Vaginal haemorrhage continued for 4 days, gradually subsiding. In all 5 pints of blood were replaced before the patient was discharged 12 days after her operation.

Section of the excised cornu revealed chorionic villi embedded in decidua. The tubal fragment was normal.

Discussion

Rupture of the uterus in this case occurred earlier than in any case of angular pregnancy so far recorded. We do not know the duration of pregnancy, for the gestation sac was not found and no clue is forthcoming from the menstrual history. It can be assumed from the size of the cavity within the cornu that pregnancy had not advanced beyond 8 weeks. Rupture only would have occurred at this time had the ovum been lodged in a space more confined than the uterine angle. It leads to the conclusion of Riddell and Scholefield (1938) that implantation is partly interstitial and partly angular. If growth occurs downwards into the uterus, pregnancy will either continue to term with the possibility of retention of the placenta in the angle, or abortion will occur. Alternatively further development may dilate the interstitial portion of the Fallopian tube when rupture will sooner or later result.

No previous case has been treated by local cornuectomy though this seemed to be obvious treatment for this patient. Should an intrauterine pregnancy follow, the question of Caesarean section will need consideration.

Finally it is now felt that a correct preoperative diagnosis could have been made in view of the clinical findings of intraperitoneal haemorrhage, together with exquisite tenderness of the uterus and profuse vaginal haemorrhage.

The latter features seldom occur with ruptured tubal pregnancy.

Summary

(1) Angular pregnancy is a rare condition though many cases have been classified as interstitial pregnancy or gestation in a uterine diverticulum.

(2) The criteria of diagnosis are pain, lateral uterine distortion and vaginal haemorrhage.

(3) A case is reported with early rupture of an angular pregnancy.

(4) Cornuectomy was performed with retention of the uterus.

(5) Though a pre-operative diagnosis of ruptured tubal pregnancy was made, consideration of extreme uterine tenderness and excessive vaginal haemorrhage should have led to a correct diagnosis.

(6) A brief review of the literature in English has been made.

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CHIARI'S SYNDROME

Report of a Case Following Pregnancy

BY

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BUDD (1846) was the first to describe the syndrome of hepatic vein thrombosis but, following Chiari's fuller description in 1899 and his account of the pathological features, it has since been linked with his name.

Less than 150 cases have been reported to date, and their rarity is exemplified by the fact that only 5 cases were discovered in 11,979 autopsies at Stanford (Armstrong and Carnes, 1944). The diagnosis is more often than not made in the post-mortem room, because its classical presenting clinical features are often masked by diseases of the liver and surrounding tissues.

A further case occurring within 3 weeks of delivery and complicated by thrombosis of the inferior vena cava below the renal veins is here recorded.

Mechanical occlusion of the hepatic veins results in gross liver engorgement with ascites, and, as demonstrated by Simonds and Jergesen (1935) in their experiments on dogs, occurs within ten to fifteen minutes of total constriction. Clinically, therefore, the syndrome may present in either an acute or chronic form, depending on whether the occlusion is total or partial. In the acute type the onset is sudden with severe epigastric pain, vomiting, and sometimes diarrhoea. Hepatomegaly and often gross ascites is evident, and the spleen is occasionally enlarged. The course is rapid and death may occur in from a few days to several weeks. Jaundice is not a feature except terminally. Males and females are equally affected, with an age range of 17 months to 70 years, the commonest being between 28 and 34 years. The onset is more insidious in the chronic form, with epigastric discomfort rather than pain sometimes radiating to the back. The initial liver tenderness quickly settles if the block in the vein re-canalizes, though further occlusion may cause aggravation of symptoms. The patient may live for a few months, though survival over several years has been recorded (Hutchison and Simpson, 1930).

CASE REPORT

A married woman, aged 25, was normally delivered of her third baby on 1st September, 1955. There was no abnormality antenatally. Labour lasted 7 hours and 10 minutes, and the puerperium was uneventful except for an explained pyrexia of 99·6° F. on the tenth day. The patient was discharged fit on 12th September, 1955, but three days later she was re-admitted to the obstetric unit with a complaint of backache, severe pain in the right groin, and sudden swelling of the right leg on arising that morning. On the previous day, apart from mild backache, she had felt well. The lochia was inoffensive and there were no urinary or colonic symptoms. There was no previous history of jaundice or of any serious illness.

On examination she was a plump, cheerful, well-looking woman in spite of her temperature of 101° F. and pulse rate of 110. The blood pressure was 150/90 mm. Hg and there was no abnormality in the heart or lungs. The liver was markedly enlarged, four-fingers breadth below the costal margin, tender, with a firm regular edge. There was a suggestion of free fluid in the abdomen. No pelvic abnormality was detected. The right thigh and calf were tense and grossly oedematous, being 3 inches larger in circumference than the left, which were normal. The following day she had pain in the left thigh and swelling of this leg developed. The diagnosis of bilateral femoral vein thrombosis was made and anticoagulant therapy was commenced. The liver enlargement was thought to be due to metastatic tumour from an unexplained primary site. This assumption was discarded when the patient remained so well in herself, with later a remission in her symptoms and slight regression in the size of her liver.

Investigations

The chest X-ray was normal. Blood cultures were sterile. The haemoglobin was 104 per cent (Haldane).

Urine tests were microscopically normal, and no pathogenic organisms were grown from the lochia. The Wassermann and Kahn tests were negative. Liver function tests were normal except that the total plasma proteins were 5·4 g. per 100 ml. (albumin 2·7 and globulin 2·3). The ascitic fluid was clear and sterile.

Course

Her pyrexia settled quickly. Penicillin and anticoagulants were given but the oedema of the right leg remained unchanged and that of the left leg increased, so that 10 days after admission both legs were grossly swollen, the left now more than the right. There was sacral oedema, and ascites made the liver difficult to palpate. Collateral venous channels were now apparent on the upper and lower abdominal wall, especially laterally, with blood flow from below upwards. Two paracenteses were performed in the following two weeks to relieve great discomfort, and sixteen pints of fluid were removed. Oedema progressed in this interval to cause enormous ballooning of the vulva requiring needling for relief and tender thrombophlebitic areas developed in the veins of the lateral abdominal wall.

Following this severe exacerbation, there was a nearly three-weeks period of remission in which the ascites remained static and the leg oedema slightly improved. The liver was firmer and regressed in size. The patient at all times was cheerful and appeared well with a hearty appetite. A high protein, high carbohydrate, low salt diet was continued throughout with 2 c.cm. Mersalyl twice weekly.

In mid-November, however, her oedema began to increase rapidly and she looked unwell for the first time. Paracenteses became increasingly necessary, producing larger amounts of fluid. Intravenous glucose and saline with potassium were given to combat dehydration as vomiting was now also a feature. She continued to deteriorate, suddenly became unconscious and died within a few hours on 5th December, 11 weeks after her admission.

POST-MORTEM

The body was that of a well-nourished woman. There was no jaundice. There was gross oedema of the legs, labia and sacral region. The abdominal cavity contained about a litre of clear yellow fluid. The right pleural cavity was obliterated by old adhesions; the left pleural cavity contained a slight excess of clear yellow fluid. The pericardial cavity was normal, as was the heart.

Both lungs were congested and oedematous and in the left lower lobe there was a recent infarct 5 cm. in diameter.

The liver was greatly enlarged, weighing 3,391 g. It was intensely congested and showed a vivid red and yellow "nut-meg" mottling of the surface and cut surface. This was more marked in the left lobe than the right (Fig. 3).

The spleen was slightly enlarged, tense, firm and congested. The other abdominal organs showed congestion and oedema only.

Both femoral veins were firmly thrombosed as were the external iliac veins which were converted into narrow fibrous cords. The inferior vena cava was similarly thrombosed up to a point 2 cm. below the entrance of the renal veins. Above this level the inferior vena cava was normal except for a small semi-circle of thrombus extending around part of its wall between the orifices of the two hepatic veins (Fig. 6). The ovarian vein on each side was greatly dilated providing a collateral venous communication between the internal iliac and left renal veins and upper part of the vena cava.

On the cut surface of the liver, the hepatic veins and their tributaries were seen to be

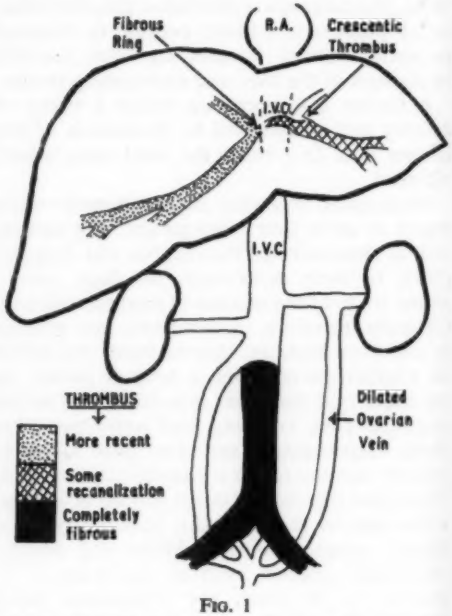

FIG. 1

Section through liver and venous system to show thrombosed hepatic veins and tributaries. Obstruction of the lower third of the inferior vena cava is also shown with compensatory dilatation of the ovarian veins.

widely thrombosed. The thrombus appeared to vary in age; on the right it was reddish-brown and recent, while on the left the thrombus was white and the vein walls thickened (Figs. 2 and 3).

As described in previous reports the hepatic veins entered the vena cava at a markedly acute angle. The right vein ran almost parallel with the vena cava to enter it at an angle of approximately 25° to a vertical line drawn through the axis of the vena cava: the left less acutely at 50°. Thromboses in both veins extended the whole length to their entrance into the vena cava, forming a small bridge of thrombus across the latter. The opening of the left hepatic vein into the vena cava was 1 cm. in diameter but the right vein suddenly narrowed from 1 cm. diameter to a pin-point orifice at the ostium (Figs. 4 and 5).

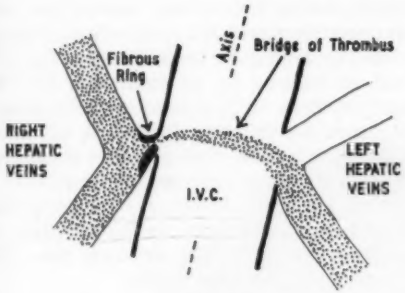

FIG. 6

To show intra-hepatic portion of inferior vena cava with hepatic veins entering it. The tiny orifice of the right hepatic vein entrance, and the acute angles the hepatic veins make with the vena cava are shown.

HISTOLOGY

Section through this tiny orifice showed a thick layer of fibrous tissue between the intima of the vein and its muscle coat. In this fibrous tissue there were many small capillary blood vessels, especially numerous near the muscle layer. This sub-intimal fibrosis was present only at the narrowing of the vein and there was a fairly abrupt transition to a normal appearance at the edge. The appearances were those of organized mural thrombus.

Sections through the hepatic veins farther out in the liver showed them to be filled with organizing thrombus, the organization being more advanced in the left lobe than the right. In some areas of the left vein there appeared to be recently formed thrombus in the centre of the vein, with a rim of older organizing thrombus around the periphery.

The liver tissue showed the changes of passive congestion with centrilobular venous engorgement and sinusoidal dilatation and some atrophy of the liver cells. There was little early fibrosis.

DISCUSSION

The case described fits well into Chiari's definition of a primary hepatic vein thrombosis.

The sudden development of acute liver enlargement with ascites in a previously healthy person should have suggested the diagnosis, though in this case the onset was more insidious and complicated by concomitant external iliac vein thrombosis.

Many cases of hepatic vein occlusion are secondary to hepatic tumours or inflammatory or necrotic processes involving the liver and surrounding tissues when these encroach on the veins; or they may be part of disease processes, such as polycythaemia, etc., which affect veins, but there is no evidence of any such process in this case. Nor is there any evidence that the thrombosis occurred as a result of endothelial damage due to hepatotoxic agents ("Bush teas", etc.), combined with protein malnutrition as occurs not uncommonly in the West Indies and parts of Africa (Bras, Jelliffe and Stuart, 1954).

Chiari himself described cases quite independent of surrounding tissue damage or disease, in which there was a primary endophlebitis of the vein wall, and he noted small subintimal areas of fibrosis at the entrance of the hepatic veins, differing only in extent from the present case in which there was a fibrous ring of tissue at the ostium of the right hepatic vein. Many theories of aetiology have been put forth to explain these lesions, none of them entirely satisfactory. Thus, in the young age groups, the presence of congenital folds or valves (Moore and Rosenblatt, as cited by Hirsh and Manchester, 1946), some error in the development of the vein wall, or

extension of the obliterative process of the ductus venosus to involve the hepatic veins (Moore and Rolleston, as cited by Hutchison and Simpson, 1930), have been suggested though without proof.

In the present case the histology shows that the lesions in the hepatic veins are more likely to be organized mural thrombus than a congenital malformation, though an underlying anomalous entry of the veins into the vena cava cannot be entirely excluded. It is an accepted fact that thromboses are more prone to occur at points of alteration of vessel calibre, and Thompson and Turnbull's postulation in 1912 that eddy currents of blood occurred at these junctions causing deposition of cells and fibrin, seems a plausible explanation. No doubt a combination of several factors is involved, and the extraordinarily acute angles the hepatic veins make with the vena cava play an important part. Kretz's (1902) theory that stress and strain at the vein junctions is a cause deserves mention. It would appear that the peculiar position of the hepatic veins in almost suspending the liver to the embedded vena cava would render them particularly susceptible to trauma and endophlebitis. It is surprising that thrombosis at this site occurs so seldom, and indeed only 3 previous cases have been reported related to pregnancy and its increased abdominal stress, and these all many weeks after delivery (Hess, 1905). Sheila Sherlock (1955), in her large series of hepatic vein catheterizations under fluoroscopy, showed that the blood flow through the hepatic veins is unaltered during pregnancy.

Mild oedema of the legs is not uncommonly found in Chiari's syndrome, but gross oedema signifies inferior vena cava thrombosis. In the above case the inferior vena cava above the renal veins had a perfectly smooth, normal wall and there was no evidence of inflammatory spread from the vein below. The crescentic thrombus (Fig. 6) in the upper third of the vena cava would appear to have arisen independently of the lower leg lesion, and its position suggested it to be a continuation of intrahepatic vein clot between the two hepatic vein entrances. In Pleasant's (1911) analysis of some 300 cases of inferior vena cava thromboses the upper third was only involved in as few as 3 or 4 per cent of cases.

The exact sequence of events in this case is almost impossible to ascertain. The initial site of block, contemporary with the patient's readmission to hospital, would appear to have been the ostium of the right hepatic vein. Blockage there must have been incomplete or of short duration. Gradually more complete obstruction of the left vein and its branches must have taken place over the next fortnight to account for the increase in clinical signs. Necrotic liver cells and fibrosis are plentiful in areas drained by this vein. The period of remission probably coincided with a certain amount of recanalization. During the fortnight before death further thrombotic extension occurred to involve the right hepatic vein and its branches, distal to the fibrous ring (Fig. 1).

No successful method of treatment of this condition has yet been found. Omentopexy and other operative procedures seem useless. Supportive dietetic regime to conserve liver function should be adhered to, as serial liver biopsies (Stuart and Bras, 1955) in veno-occlusive disease have shown that recovery of liver cells can occur if obstruction is short-lived and stops at the congestive stage. Anticoagulants are worthy of a more extensive trial; in this case Tromexan was unfortunately discontinued during the phase of remission, and this may or may not have influenced the subsequent course.

Summary

A case of Chiari's disease with stenosis at the entrance of the right hepatic vein into the inferior vena cava is described. It followed three weeks after a normal confinement, and was complicated by inferior vena cava thrombosis. A review of suggested aetiological factors is made and the treatment of the condition discussed.

I wish to thank Mr. H. J. Drew-Smythe for permission to publish this case and Dr. John Naish for his guidance and help in preparing this article. I am also indebted to Dr. N. J. Brown for his great assistance in preparing and interpreting pathological data. Acknowledgments are also due to Mr. W. G. Sweet for photographs produced.

FIG. 2

Section through liver to show occluded hepatic veins. Recent thrombus is seen on the right, and old fibrous in the thickened left vein.

FIG. 3

Section through liver to show atrophic liver cells and fibrous replacement chiefly in left lobe. The occluded hepatic veins are again seen, with re-canalization in the left thrombosed vein.

FIG. 4

Intra-hepatic portion of inferior vena cava opened out to show minute right hepatic vein orifice. Adherent clot is seen at the opened entrance of the left hepatic vein.

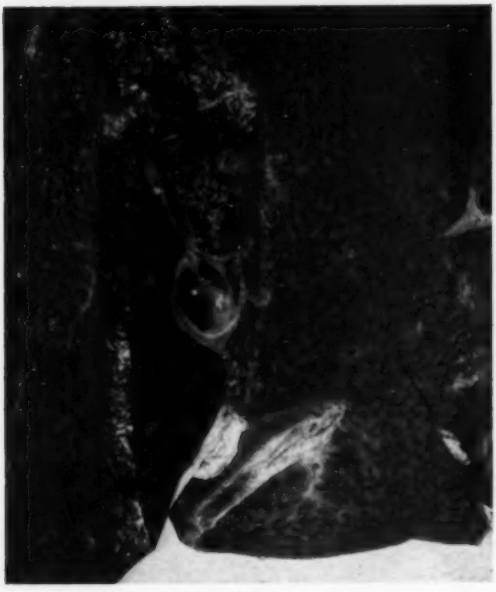

FIG. 5

Section through liver to show right hepatic vein just distal to its minute pin-point (needle marking) opening into the vena cava. A fibrous ridge of tissue is seen before the vein widens.

I.M.K.

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VAGINAL DECIDUOSIS SIMULATING CARCINOMA

BY

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ONE of the less common histological changes occurring in the genital tract during pregnancy is a decidual transformation of certain hormone-sensitive stromal cells in sites other than the uterine decidua and apart from areas of endometriosis (Novak, 1952).

This ectopic decidual reaction is not infrequently seen in the stromal cells of the cervix and vagina, but is rarely of clinical significance. In recent years, however, a few cases have been reported in which an unusual type of decidual reaction has given rise to lesions closely resembling cervical or vaginal carcinoma.

Hennessy (1943) reported a cervical tumour, clinically indistinguishable from early carcinoma, in a 46-year-old para-5 at the fourth month of pregnancy. Biopsy of the tumour showed the histological appearance of marked decidual reaction with no evidence of malignancy.

In a case reported by Klein and Domeier (1946) a friable growth of the cervix in a 23-year-old primigravida at term was shown histologically to be composed of papillary masses of decidua, and in another described by Bowles and Tilden (1951) biopsy of an indurated ulcer of the cervix in a 38-year-old multipara at the eighth month of pregnancy showed only a pronounced decidual reaction.

Three similar cases of deciduosis were reported by Lapan (1949). Two of these occurred in the cervix and one in the posterior vaginal fornix, and all three were clinically indistinguishable from carcinoma. One of the cervical lesions was found in a 31-year-old para-1 with 2-weeks amenorrhoea and histological confirmation of "anaplastic carcinoma" was given by a pathologist before he was aware of the coexistence of an early pregnancy.

The very few instances reported indicate the rarity of this condition, but a further case was recently seen and is reported below.

CASE REPORT

Mrs. P.E., a 39-year-old para-2, attended the Antenatal Clinic at Edgware General Hospital with a history of 25-weeks amenorrhoea.

Previous History. The menarche occurred at the age of 13 years and her menstrual cycle was regular, 5/24. In 1942 she had a spontaneous vertex delivery of a premature male infant weighing 5 pounds, which died after 5 hours, and in 1944 an assisted breech delivery of a healthy female infant weighing 8 pounds 12 ounces. Dilatation and curettage had been performed in November, 1954 for functional uterine bleeding.

Present Pregnancy. The patient's last menstrual period commenced on 23rd July, 1955 and she was first seen in the clinic on 18th January, 1956.

General physical examination revealed no abnormalities. Her blood pressure was 130/70 and the urine contained no abnormal constituents. The Wassermann reaction was negative. Abdominal examination confirmed a pregnancy of about 28-weeks duration.

Apart from slightly excessive size of the uterus pregnancy had been uneventful so far but the passage of a Sims speculum provoked slight fresh vaginal bleeding. On inspection a polypoid growth was seen at the vaginal vault and from this the bleeding appeared to originate. A provisional diagnosis of carcinoma of the cervix was made and the patient admitted to hospital for investigation.

The vaginal bleeding ceased spontaneously following admission and 2 days later examination was carried out under general anaesthesia. The vulva and lower vagina were healthy, but a large polypoidal and friable growth was seen occupying the posterior and left lateral vaginal fornices. The cervix was completely uninvolved. Pressure with the speculum on the growth provoked fresh vaginal bleeding. Rectal examination revealed no parametrial thickening or rectal involvement. A diagnosis of carcinoma of the vagina was now considered and a biopsy specimen taken from the edge of the growth.

The pathologist reported as follows: "Section shows a thick band of decidual tissue, not covered by squamous epithelium, lying on a very vascular loose connective tissue. Vaginal ectopic decidua" (Fig. 1).

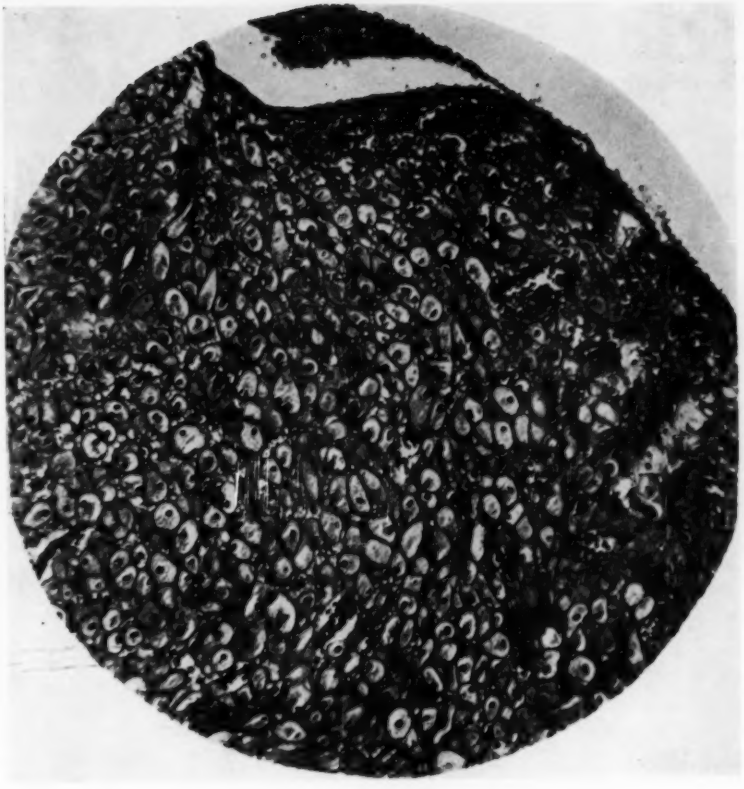

FIG. 1
Vaginal Deciduosis. ×150.

The patient was discharged from hospital to attend the Antenatal Clinic. No further vaginal bleeding occurred during pregnancy. At the 34th week of amenorrhoea a mild degree of hydramnios was found. Straight X-ray showed a single foetus, of at least 38-weeks maturity, presenting by the vertex and no foetal abnormalities were apparent. One week later she was admitted to hospital with a mild pregnancy toxaemia and labour was induced by hindwater rupture when 4 pints of liquor amnii were drained off. At the time of induction fresh bleeding occurred from the vaginal tumour which was unchanged in appearance. Spontaneous vertex delivery of a healthy male infant weighing 8 pounds 6 ounces occurred 13 hours later. There was no abnormal post-partum bleeding and the placenta was healthy.

The puerperium was uneventful and speculum examination on the 12th day showed only a few discrete nodules in the posterior vaginal fornix.

Examination of the patient in the Postnatal Clinic 6 weeks after delivery showed a completely normal cervix and fornices with no trace of the pre-existing vaginal lesion.

Discussion

It is clear that on rare occasions an excessive decidual reaction may occur in the cervix or vagina during pregnancy and give rise to a polypoid mass or an indurated ulcer in these areas.

The main interest of this condition is its rarity and its macroscopic similarity to carcinoma. In all the reported cases a clinical diagnosis of carcinoma was made, the true nature of the lesion being revealed only on histological examination. In one of Lapan's cases an incorrect histological diagnosis of carcinoma was also made but this would only be likely to occur if the pathologist was unaware of the coexistence of pregnancy or was unacquainted with ectopic decidual reactions.

These lesions have been discovered at all stages of pregnancy, from the 6th week up to term. Apart from vaginal bleeding they have caused no trouble during pregnancy and have not interfered with vaginal delivery in the reported cases. They require no specific treatment and, as would be expected, undergo rapid spontaneous regression following parturition.

In the case reported here the discrepancy between the period of amenorrhoea and the size of the foetus may have been due to bleeding from the area of deciduosis at the time of the recorded last menstrual period.

Summary

A case is reported in which an unusual type of decidual reaction simulated a malignant vaginal tumour during pregnancy and similar cases appearing in the literature are reviewed.

Acknowledgments

I am grateful to Dr. Muriel Rose and Mr. E. ap I. Rosser of the Department of Obstetrics and Gynaecology, Edgware General Hospital, for their permission to publish the case history and advice in the preparation of the text. Thanks are also due to Dr. J. L. Hamilton-Paterson for the pathological report and photomicrograph.

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ESCHERICHIA COLI PSEUDOMEMBRANOUS ENTEROCOLITIS

Post-operative Complication of Hysterectomy

BY

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WITH the advent of modern therapeutic procedures post-operative complications of hysterectomy are becoming more rare. Recently attention has been drawn to fatal enterocolitis as a rare complication at this time (Fowler, 1955). The following example of this condition has recently been under my care.

The patient, aged 46, para-3, was admitted suffering from menorrhagia and metrorrhagia for the previous 2 years. She had had 3 normal full-time deliveries and no miscarriages. The last pregnancy was in 1948. Her periods had been regular until the onset of her complaints, which had been treated by curettage of the uterus 6 months prior to the present admission. No gross pelvic lesion had been found; the uterine curettings had shown endometrium in the secretory phase. Following the curettage there was no improvement in the severity of her uterine bleeding and she was admitted for hysterectomy.

She had always been well in the past and gave no history of gastro-intestinal disease. She had, however, been treated with penicillin and bismuth from 1951–1954 for a syphilitic infection. There had been no change in the W.R. and Kahn tests of her blood despite the treatment given.

On examination her general condition was good. Heart and lungs were normal. Spleen and liver were not palpable, nor were there any abnormal findings present on abdominal palpation. Her blood pressure was 120/70 mm. Hg and her haemoglobin was 80 per cent.

Five days after admission total hysterectomy and bilateral salpingo-oöphorectomy were carried out without difficulty under general anaesthesia (pentothal, nitrous oxide and ether, and oxygen), the operation lasting 45 minutes.

She was very well on the first post-operative day, the temperature, pulse and respiration being normal. She was not given any drugs except ferrous sulphate, gr. 6, t.d.s. On the second day, about 36 hours after the operation, she complained of abdominal pain and passed some loose stools. She passed about 5 motions in 8 hours, each copious in amount and very offensive. There was no nausea or vomiting. On examination no abnormality was found. Her temperature was normal and so too was her pulse rate. The stools were watery and dark in colour; no blood could be seen on inspection. The iron tablets were discontinued. Twenty-seven hours later she had 3 more motions of the same nature, each accompanied by severe colic. When she was passing the last motion she suddenly collapsed; her skin became cold and clammy. The pulse was practically imperceptible. Her blood pressure was 70 mm. Hg systolic with the diastolic unrecordable. There was peripheral cyanosis, breathing was sighing in nature and the abdomen was soft and not distended. Oxygen inhalation, intravenous methidrine, 30 mg. in 1·5 ml. and intravenous dextran drip were administered. Her condition improved for the next hour when she passed another motion of the very offensive dark watery stools. She then became irrational and pulled out the intravenous drip from her arm. A cut-down in her legs was carried out and 5 per cent glucose in normal saline was given. Her abdomen by then had become distended. The pulse became weaker and the blood pressure was unobtainable. Levophed, 4 ml. in a litre of normal saline, was given in an attempt to resuscitate the patient, but she never recovered and died 43 hours after the onset of the first symptoms. The culture of the stools passed showed a pure growth of *Bacterium coli communis*.

Summary of Necropsy Findings (Dr. A. C. Counsell)

The body was that of a well nourished woman. Petechial haemorrhages were present in visceral pleura and pericardium; otherwise heart and lungs were healthy.

The gastric mucosa was also the seat of petechial haemorrhages; apart from this it was normal. There was a membranous covering of the gut mucosa from about half way down the jejunum to the rectum. On stripping off the membrane the mucosa was hyperaemic and showed loss of lustre. Liver, kidneys, spleen and adrenals showed no naked eye abnormality.

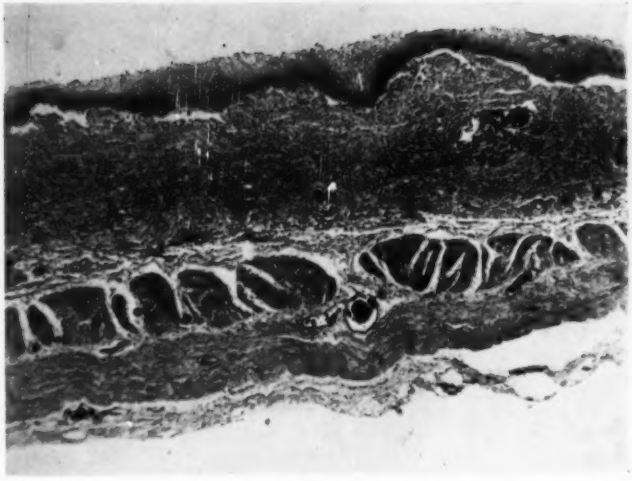

FIG. 1

Pseudomembranous enterocolitis. Haematoxylin and Eosin. ×35.

Some subperitoneal haemorrhage was seen over the posterior surface of the bladder and in the operation area, but there was no evidence of infection.

Histology (Fig. 1). Sections of the intestine showed a fibrinous exudate on the surface, with necrosis of gland tubules of the mucosa and a dense infiltration of the substantia propia by lymphocytes, plasma cells and histocytes.

Comment

The occurrence of pseudomembranous enterocolitis has been known for a long while. Penner and Bernheim (1939) stated that they were unable to find an explanation for acute pseudomembranous enterocolitis, although it is recognized that similar lesions are found in uraemia, certain toxic infections and poisoning from arsenic and mercury. They believed that a vasomotor upset following operative trauma may be a major factor in the pathogenesis of the lesion. In the reported case the patient was in a fit condition to undergo the operation which was a straightforward and easy hysterectomy with no interference with the bowel.

In most of the cases described the staphylococcus has been incriminated as the offending organism, especially so after antibiotic administration. Todd and Hopps (1955) laid down 3 aetiological requirements: (1) the antibiotic drug must be ineffective against the infecting staphylococcus; (2) it must be lethal to the normal flora of the gut and (3) it must be given by mouth. In this case none of these postulates is fulfilled as in pure culture the organism grown was the *E. coli* and there had been no antibiotic administered. It is difficult to incriminate the penicillin she last had a year ago for her syphilitic infection, as an aetiological agent.

A review of the reports of hysterectomies performed in the United States, South Africa and China showed that this complication has not been previously recorded. Most of the cases reported occurred after gastro-intestinal surgery and not gynaecological.

The appearance of an unexplained severe circulatory collapse is the cardinal picture of the condition. There may have been acute cramping diffuse abdominal pain with or without diarrhoea preceding the collapse.

In established cases energetic treatment is directed to combat the severe shock with adequate fluids and to maintain the electrolyte balance as for a case of cholera. The use of an antibiotic—erythromycin—has been advocated; it is a relatively new drug and hence the chance of any organism being resistant to it is less.

It must be pointed out that though in this case only the *E. coli* was grown in pure culture there is the possibility that the staphylococcus might have played a part. We had this in mind and bacteriological studies were directed towards isolating this organism, but none was grown in the culture from the stools passed from specimens collected at the post-mortem examination.

I am greatly indebted to Mr. C. W. F. Burnett for help and encouragement, and both to him and Mr. D. A. Davies for permission to publish. I wish also to thank Dr. A. C. Counsell for the necropsy summary and the photograph of the section.

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MONO-AMNIOTIC TWIN PREGNANCY WITH TWISTING OF THE CORDS

A Case Report

BY

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MONO-AMNIOTIC twin pregnancy is rare and Quigley (1935) quotes Dietrich as saying, "It is given no obstetrician to see more than one case in his experience." The incidence of the condition has been variously estimated by Muller at 1 in 6,000 and at 1 in 60,000 by Rosenberg (as quoted by Boyle and Richter, 1947). King *et al.* (1952) reported 5 cases occurring in New Orleans in a period of 18 months. During the years 1952 to 1955, inclusive, a total of 930 cases of twins were delivered in the Kandang Kerbau Hospital, Singapore.

CASE REPORT

The patient was a European aged 38 years and this was her second pregnancy. She was referred to the writer by a general practitioner on the 23rd July, 1956 when he confirmed a diagnosis of twin pregnancy radiologically. She had been delivered normally 3 years before of a full-time living female child.

Her last menstrual period was on the 21st November, 1955 and the expected date of confinement was calculated to be the 28th August, 1956. She had felt reasonably fit throughout the pregnancy though when seen at hospital she complained of some upper abdominal discomfort. On examination the size of the uterus was larger than it should have been for the period of gestation and palpation was difficult. One foetus was presenting by the head and the other was felt lying obliquely. At no time during the antenatal period was her blood pressure or urine abnormal and there were never any toxic symptoms or signs.

On the 30th July, 1956 her condition was satisfactory and both babies seemed to be presenting by the head. Foetal movements were felt and no attempt was made to specifically auscultate two foetal hearts. A week later, when 37 weeks pregnant by her dates, she was seen again and at this time most of her abdominal discomfort had gone. On examination the uterus felt a little smaller. This was quite puzzling. The presentation of the twins was the same as before and foetal movements were felt. A foetal heart was heard without difficulty and the other was presumed to be present.

The next day, about 4.30 p.m., the patient noticed a small amount of dark coloured watery fluid coming from the vagina. She presumed her membranes had ruptured and two hours later was admitted to hospital. On examination then the uterus was contracting and felt tense. She was draining a lot of darkly stained liquor amnii from the vagina. On vaginal examination the cervix was effaced and admitted three fingerbreadths. Engaging tightly in the pelvic brim was the vertex of one foetus and the face of the other. The foetus presenting as a face felt macerated and the other felt normal. A foetal heart was heard with difficulty. It was slow in rate and irregular in rhythm.

It was obvious that one of the twins, for some reason, had died *in utero* and that the other was distressed. In view of this it was decided to terminate the labour by lower segment Caesarean section. This was carried out under general anaesthesia at 9 p.m., 4½ hours after the rupture of the membranes.

On opening the uterus there was a small amount of greenish brown liquor amnii still present. A macerated child presenting as a face was delivered first. The second twin, presenting as a vertex, was then delivered breech first. This baby was limp and blue but responded to rescuscitative measures. Bleeding was minimal and the placenta was expressed. It was noted to be single with a battledore insertion of the cords to its lower margin. The cord to the dead foetus showed evidence of maceration and about half way along its length there was a loop, tightly twisted and encircling the cord to the living child (Figs. 1 and 2). The foetal surface of the amnion presented no signs of septal remains or any other indication that a membraneous septum ever existed.

Both babies were female. The living infant weighed 5 pounds 3 ounces (2,490 g.) and the macerated twin 3 pounds 4 ounces (1,560 g.). The patient's convalescence was uneventful and the surviving twin was breast-fed.

COMMENT

There are two main theories regarding the cause of mono-amniotic twins (Quigley, 1935). One is the theory of primitive duality. This maintains that there are originally two amnions and that the two cords lying together on either

FIG. 1
Photograph showing the placenta and twisted umbilical cords.

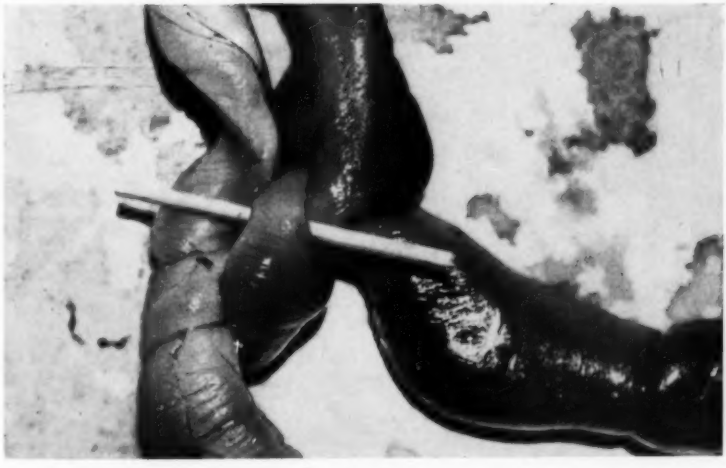

FIG. 2
Photograph of the loop of one cord encircling the other umbilical cord.

side of the partition cause it to rupture as a result of their pulsations. The other theory, that of primitive unity, maintains that during early development the two blastodermic vesicles meet and join and are enveloped by one amnion.

The chief clinical interest is the danger of death of one or both of the foetuses from twisting or knotting of the umbilical cords. This is very common and occurred in this case. Most writers are of the opinion that knotting occurs at the ninth to twelfth week of gestation, at which time the cords are sufficiently long and the foetuses small and active. In Quigley's (1935) series of 109 cases torsion or true knot formation was noted in 53·2 per cent of cases. Both twins survived in only 17 out of the 109 cases. The corrected foetal and neonatal mortality for this series was 68 per cent.

In the case described the twisting of the cord had produced intra-uterine death of one foetus before labour. This is an exception to the popular belief that loops drawn tightly enough to cause foetal death occur only during labour. The loop encircling the other cord was being drawn tighter during the early labour and embarrassing the circulation along the second cord as was shown by the disturbed foetal heart. It is felt that the Caesarean section was just in time to prevent the loss of the second twin.

There is no method by which the presence of this rare condition can be diagnosed before delivery and if it is considered it is rarely made sufficiently early to be of any value.

Summary

A case of mono-amniotic twins with twisting of the umbilical cords is described.

Two theories attempting to explain the condition are briefly mentioned.

The prognosis for the foetuses is unfavourable and there is no method of definitely diagnosing the condition before delivery.

Acknowledgments

My thanks are due to Mr. Austin Bennett for the photographs.

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VAGINAL DELIVERY OF FULL-TIME CONJOINED TWINS

BY

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A CASE of conjoined twins delivered vaginally at term is presented because of the difficulty in establishing the complete diagnosis, the union of the infants being discovered only during the delivery, and because of the comparative ease with which this delivery was accomplished.

CASE REPORT

The patient, who had had one previous normal pregnancy and delivery, was referred to the antenatal clinic on 30th January, 1956 for confirmation of a twin pregnancy. The last period had commenced on 10th June, 1955, though she had noticed a slight blood loss in the following month, and, as the menstrual cycle was normal, delivery was expected on 17th March, 1956.

Abdominal examination showed the uterine fundus to be 2 fingersbreadth below the xiphisternum, and the girth measured at the level of the umbilicus was 39 inches. One head could be felt in the lower pole of the uterus freely movable above the pelvic brim. Foetal parts were palpable all over the rest of the uterus, but only one foetal heart could be detected. Blood pressure and urine examination were normal.

The presence of a multiple pregnancy was suggested by the abdominal examination, and this was confirmed radiologically. Both twins presented by the vertex, with the right twin leading, and the maturity was estimated at 30 to 32 weeks (Fig. 1).

The patient was referred to her own doctor, and arrangements made for her delivery in a nursing home.

On 8th April, 1956, when 43-weeks pregnant according to the date of the last period, the patient again attended the clinic. Foetal movements had ceased 3 days before, and her doctor had been unable to hear the foetal heart. On this occasion the fundus of the uterus reached to the level of the xiphisternum, and the uterus was greatly distended. The head of the leading twin was deeply engaged in the pelvis. No foetal heart sounds could be heard. An X-ray examination was arranged for the next day but late that evening the patient was admitted to hospital in labour.

Labour had already been in progress 4 hours, the contractions were strong, and on rectal examination the cervix was found to be 4-fingers dilated with the foetal head at the level of the ischial spines. Pethidine 100 mg. was given. This was soon followed by rupture of the membranes, and 1 hour later the foetal head was visible.

After half an hour the head of a macerated child was born, and, though some difficulty was encountered in delivering the shoulders, this was accomplished. Thereafter, however, strong traction failed to deliver the child further than the chest, and at this point I was summoned.

Abdominal palpation showed one head in the left hypochondrium, and no obvious contraction ring. As vaginal delivery failed to reveal a cause for the delay in delivery, the patient was anaesthetized. A hand was passed into the uterus and again no contraction ring was felt and a leg was brought down after performing a large episiotomy. It was then possible to bring down the second leg, and with traction deliver the child as far as the umbilicus when it was found that exomphalos was present, but further progress was not possible. At this stage the first child was delivered completely apart from the pelvis. Vaginal examination now revealed the presence of further limbs but no separate breech, and the diagnosis of conjoined twins was established.

As the twins were dead it was decided to attempt vaginal delivery. The second pair of

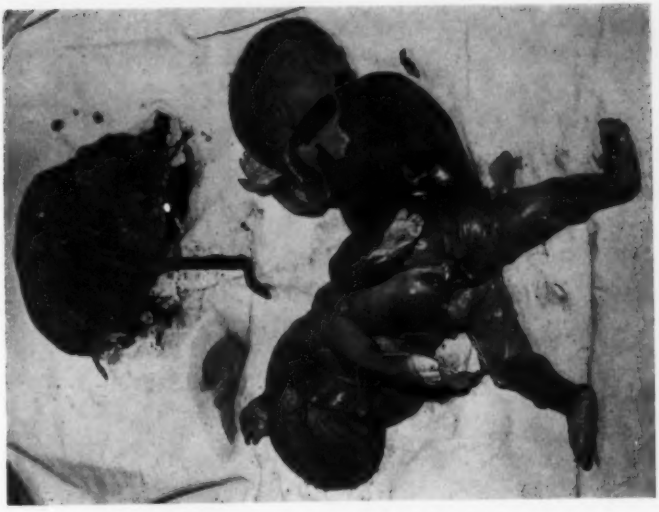

FIG. 2

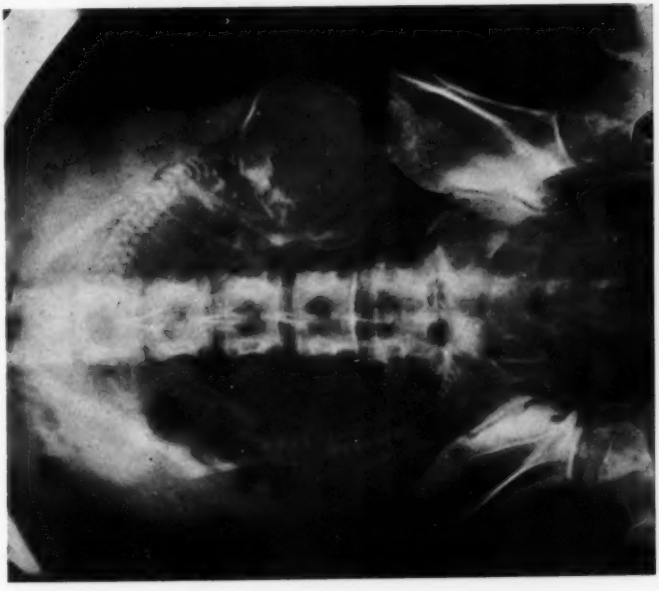

FIG. 1

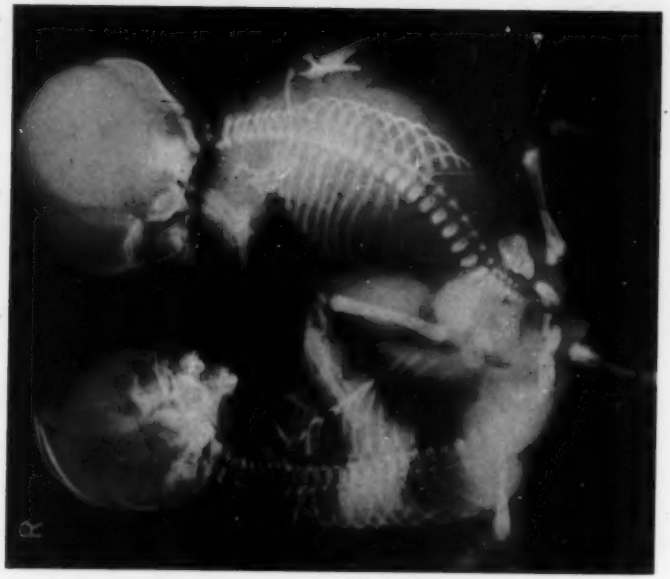

FIG. 4

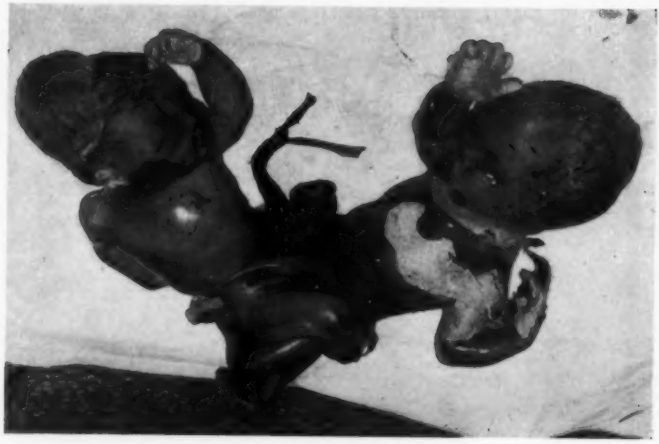

FIG. 3

D.K.

legs were then brought down, and at this stage it was seen that the union extended from the umbilicus to the perineum. The trunk of the second child was easily delivered by traction, and the head by the Mauriceau Smellie Veit manœuvre.

After manual removal of a placenta weighing 2 pounds 2 ounces, the uterine cavity was carefully palpated for tears, the cervix was inspected, and the episiotomy repaired. Apart from slight anaemia the patient had an uneventful puerperium and was discharged home on her 10th day.

A dissection of the specimen was undertaken by Dr. Sharp of the Anatomy Department of the University of Leeds, to whom I am indebted for this summarized report. The twins (ischiopagus) were fused at the perineum and lower part of the anterior abdominal wall and shared a common umbilical cord 34 inches in length (Figs. 2 and 3). Their combined weight was 14 pounds 2 ounces. No external genitalia were present and there was a single anus and rectal canal. The thorax and vertebral column in each twin were normal, and an X-ray examination showed no bony union (Fig. 4).

Each foetus had a normal liver, spleen, stomach, small intestine and pancreas. The small intestine of each was continuous with a common large intestine at a T-junction, but the large intestine was short, with no caecum or appendix, and opened by a normal rectum into the anal canal. There was a single large kidney in one foetus and two kidneys in the other. Two bladders were present, and both opened into the common rectum. As no gonads were found in the abdomen, they were sought elsewhere, and subsequently a small nodule of tissue resembling a testicle was found in the inguinal region of one foetus. Histological examination showed it to contain seminiferous tubules.

Comment

Rawlings and Warwick (1950) reported a case of omphalopagus which was similar to this one, in that an X-ray during pregnancy gave no indication that conjoined twins were present, and also in that the delay occurred near the end of the second stage of labour. It has been claimed by Graber (1945) that the condition can be diagnosed on X-ray by the fact that the two heads are at the same level, but this was not so in this case.

The diagnosis was made difficult only by the fact that the possibility of the condition did not occur to me and I was thinking of a contraction ring or a large sacral tumour of the first child. The delivery was surprisingly easy, but I would not like to have been presented with the problem with living twins.

I have to thank Professor A. M. Claye for his permission to publish this case and also Mr. W. Blackledge of the Department of Photography for the illustrations.

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ENDOMETRIOSIS, ADENOMYOSIS AND PREGNANCY

BY

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A REVIEW of the literature suggests that pregnancy associated with endometriosis is infrequent partly due to the late age incidence of the disease and partly due to the pelvic pathology associated with it. Reynolds and Maccomber (1942) quote 88 per cent as the normal fertility in marriage. This contrasts markedly with the relative sterility rate of 53 per cent in women suffering from endometriosis reported by Haydon (1942).

Scott (1944) made a study of forty-seven reports on endometriosis associated with pregnancy and added two of his own. The ultimate results were ascertained in only 31 cases, amongst which were 12 cases of adenomyosis and 19 cases of diffuse pelvic endometriosis. In the 12 cases of uterine endometriosis, there was spontaneous rupture of the uterus in 3 cases, post-partum haemorrhage in 3 and dystocia in 2 cases. Complications were less frequently met with in pelvic endometriosis with an unaffected uterus. Thus out of 19 cases there was 1 case each of rupture of an ovarian endometrial cyst, a ruptured ectopic pregnancy in the same ovary with endometriosis, and 1 case of dystocia. Other complications were 7 cases of abortion and 2 more cases of ectopic pregnancy in the whole series of 47 reports.

Lock and Myers (1946) reported 2 cases of endometriosis in which patients were treated conservatively. Subsequently both conceived and had a normal pregnancy, delivery and puerperium. There are many similar reports to be found in the literature.

Conservative treatment has been advocated in women of childbearing age with endometriosis. Novak (1931) referred to the well-known fact that many patients had complete relief of symptoms after a conservative operation. He mentioned two patients seen in one year in whom unilateral cysts were removed and pregnancy followed in both cases before the recurrence of symptoms necessitating another operation.

Bacon (1949) reported the results in 138 cases of pelvic endometriosis treated by conservative surgery. Of these, 30 (26·8 per cent) conceived and had living children after operation.

Ware (1950) presented 13 cases of pregnancy in which endometriosis was proved by operation either before or during gestation. There were 2 cases of abortion and the others were delivered at term with no complications.

Gainley, Keeler and Nicolay (1952) reported 38 cases of pregnancy associated with endometriosis and noted improvement in most of them after delivery. Other writers have reported the same long-term relief of symptoms, even in very widespread disease, after a successful pregnancy. Among Gainley's cases there was almost total involution in a patient with extensive recto-vaginal endometriosis. The complications were abortion in 6 cases, torsion of an ovarian endometrial cyst and one case of ovarian pregnancy with a nidus provided by endometriosis.

Brewer and Maher (1954) found symptomatic relief in cases of endometriosis treated with oestrogen or androgen and many became pregnant before surgery was called for. It was their opinion that, when endometriosis was encountered during an abdominal operation, approximately one-third of the patients would subsequently conceive if conservative procedures were adopted provided that there was no other cause of sterility.

Of the cases reported above only 13 were uterine disease *per se*, the rest were all pelvic endometriosis associated with pregnancy. There

was only one operation (fundectomy) done on the uterus followed by pregnancy (Lock and Myers, 1946). This infrequency is probably accounted for by the fact that when surgery is indicated for adenomyosis hysterectomy is the usual procedure. Of 112 cases of adenomyosis operated upon by the Staff of the Department of Obstetrics and Gynaecology, Hong Kong University, from 1948 to 1954, conservative surgery was possible on only 2 occasions; one of these patients remains sterile and the other subsequently became pregnant.

Case Report

Mrs. C.P.S. (Case No. 258/51), aged 29, was admitted to Queen Mary Hospital on 1st April, 1951. She had been married for 3 years and had had 2 abortions, the last of which had occurred 2 years previously. Her menstruation was normal until after the last abortion when she started to have progressive dysmenorrhoea and menorrhagia.

On abdominal examination a mass, which was fixed but not tender, was found arising from the pelvis and extending half way to the umbilicus. Pelvic examination revealed that the mass sprang from the uterus which was firm and enlarged to the size of a 4-months pregnancy. The fornices were clear and the cervix normal.

At laparotomy the whole uterus was more or less uniformly enlarged with the exception of the left cornu where a smooth mass measuring $5 \times 4 \times 4$ cm. projected upwards. The tubes and ovaries were normal. An attempt was made to enucleate the mass but as it was neither encapsulated nor circumscribed such a procedure could not be done. About one-half of the body of the uterus including the interstitial portion of the left tube had to be amputated. There were multiple chocolate-coloured areas scattered throughout the whole thickness of the uterine wall which was about 3 cm. in thickness. After implanting the remaining portion of the left tube and suturing the uterine wound the size of the uterus was about twice that of normal. Microscopic examination confirmed the diagnosis of adenomyosis.

The menstrual flow was normal after operation but dysmenorrhoea persisted. The patient became pregnant 3 months later and attended the antenatal clinic regularly. At the 38th week of pregnancy there was an asymmetrical enlargement of the uterus which bulged prominently upwards and outwards on the left side. Foetal parts could be felt with greater ease in this area than over the rest of the uterus. An elective Caesarean section was done at this juncture because it was felt that rupture of the uterus might take place if the pregnancy was allowed to continue.

The fundus and the left side of the uterus were found to be replaced by a protruding sac covered by a thin layer of fibrous tissue which justified the suspicion of imminent rupture.

A longitudinal incision was made in the uterus and a living male baby weighing 6 pounds 3 ounces (2,840 grams) was delivered. There was no residual endometriosis in the uterine wall.

In the last follow-up examination, 3 years after delivery, the patient was found to be in good health. Menstruation was regular and the flow normal. Dysmenorrhoea had since disappeared. Examination revealed that the uterus was about half the normal size, and the appendages were not palpable.

Discussion

It is interesting to note that in this case endometriosis became clinically manifest after two pregnancies, both of which ended in abortion. The process was apparently completely arrested after the operation of fundectomy, and the patient embarked upon a third pregnancy which was terminated by Caesarean section at the thirty-eighth week on account of the risk of rupture of the uterus. The sacculation which occurred at the scar on the left side of the uterus might be attributed to the fact that the patient became pregnant too soon after operation. Lock and Myers (1946) reported a case of endometriosis where a fundectomy was done and approximately two-thirds of the corpus uteri was removed. Two years later this patient, after an easy labour, was delivered vaginally of a living female child weighing 6 pounds 2 ounces (2,780 grams). It must be realized that there is a definite hazard of rupture in these cases after such an extensive operation on the uterus.

Summary and Conclusion

From the analysis of the reports on pregnancy associated with endometriosis it has been noted that pregnancy occurs in approximately one-third of cases after conservative treatment. This treatment may be medical or surgical. The symptoms are relieved completely or partially in over one-half of the cases. Complications arising out of pregnancy are more often met with in uterine than in external endometriosis.

A case of fundectomy for adenomyosis followed by normal pregnancy and involution of the lesion is here presented.

When surgery is indicated for endometriosis and when the childbearing function is to be preserved in young patients a conservative operation is the one of choice. This can and should be done even in the presence of considerable endometriosis. Pregnancy has no

adverse effects on the lesion, indeed the contrary finding is the usual one.

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PREGNANCY AND PARTURITION IN ASSOCIATION WITH DIABETES INSIPIDUS

BY

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As the occurrence of pregnancy in the presence of diabetes insipidus, an uncommon condition, is unusual, this case is reported to show the possible effects on pregnancy and labour.

CASE REPORT

Mrs. G.P. was aged 33 years.

Previous Obstetric History. Six full-term babies of weights from 6 to 7 pounds were delivered spontaneously after labours of from 14 to 16 hours. There had been one miscarriage. One child had died of congenital heart disease. Following the last delivery in June, 1952 there had been a third-stage haemorrhage necessitating blood transfusion with a further transfusion of packed cells in the puerperium for the correction of anaemia.

Previous Medical History. In March, 1954 the patient developed iridocyclitis and parotitis (Haerfordt's Syndrome) and was treated with topical cortisone 1 per cent and atropine 1 per cent eye drops. This condition persisted intermittently for 2 years and was associated with joint pain in the hands and knees.

In October, 1954 the patient reported to the antenatal clinic on account of 3-months amenorrhoea when no pregnancy was found and subsequent endometrial biopsy revealed a normal secretory endometrium. At this time the patient had noticed an excessive output of urine. The fluid intake and output over 24 hours were as follows:

Intake:	3,080 ml.	1,847 ml.	1,987 ml.
Output:	4,424 ml.	5,946 ml.	5,208 ml.

The urine had a specific gravity of 1,002 in the first morning specimen and contained no abnormal constituents.

Further investigation was postponed because of domestic difficulties until January, 1955 when the patient was admitted to the medical department of Dumfries and Galloway Infirmary.

Investigation revealed the following:

Blood

Haemoglobin:	91 per cent Sahli. (13·5 g. per cent)
Red blood cells:	4·7 million/c.mm.
White blood cells:	4,500/c.mm.

A blood film showed no abnormality.

Blood sedimentation rate:	5 mm./hour
Wassermann reaction:	Negative
Blood pressure:	120/70
Blood group:	0, Rhesus positive

Blood Sugar Curve

	Fasting	½ hr.	1 hr.	1½ hr.	2 hr.	2½ hr.
Blood sugar mg. per cent	120	240	240	180	120	120
Urine ..	Nil	Nil	Nil	Nil	Nil	Nil

"A high lag curve."

Chemistry

	mg. Per cent		Per cent
Serum sodium	325	Blood urea	20 mg.
Serum chloride	560	Total protein	7·2 g.
Serum cholesterol	114	Albumin	5·1 g.
Serum potassium	20	Globulin	2·1 g.
Serum calcium	12		

The basal metabolic rate was —0·4 per cent of normal. The Mantoux test was negative.

Water Excretion Test

One pint of water taken at 6.15 a.m.

Time	Volume in ml.	Specific Gravity
6 a.m. ..	90	1,004
7 a.m. ..	90	1,003
8 a.m. ..	150	1,001
9 a.m. ..	146	1,002
10 a.m. ..	86	1,004

The urinary excretion of 17-ketosteroids was 1·47 mg. per cent. X-ray of the chest showed enlargement of the hilar shadows, and X-ray of the skull and hands showed no abnormality.

The diagnosis was made of sarcoidosis involving the lungs, eyes and the posterior pituitary gland.

During the time spent in the medical department there was an exacerbation of the iridocyclitis and joint pain. Cortisone and atropine eye drops were resumed and aspirin was given as required.

Initially the urine output was controlled by the subcutaneous administration of pitressin, 10 units thrice daily, and thereafter pitressin tannate was tried; but finally thirst and polyuria were controlled by one capsule of Di-sipidin inhaled at noon daily. Di-sipidin contains 300 units of anti-diuretic factor per gramme and each capsule contains 0·1 g.

Present Pregnancy. Following diagnostic curettage in December, 1954 the menstrual cycle had been irregular until September, 1955. On attendance at the medical clinic in May, 1956 for routine follow up an 18-weeks pregnancy was discovered and the patient was referred for antenatal advice.

The patient was well and thirst and polyuria controlled by the Di-sipidin snuff. Examination of the abdomen revealed a pregnancy of some 18-weeks duration. The blood pressure was 130/80 and the urine free from abnormal constituents.

The pregnancy continued uneventfully and at the thirty-fourth week the presentation was found to be breech, X-ray examination confirming a single normal foetus of some 34-weeks maturity with one leg extended and the other flexed.

At this time the patient had an exacerbation of the joint pain and was admitted to Cresswell Maternity Hospital for rest.

During her 3-weeks stay in hospital prior to delivery the patient had strong uterine contractions for about two hours each afternoon and it was noticed that these began shortly after the snuff was taken at midday. Accordingly the inhalation of the Di-sipidin was abandoned temporarily. It was thought that the diabetes insipidus might be controlled by increased activity of the posterior pituitary during the pregnancy but on stopping the snuff the thirst and polyuria returned and the fluid balance was as follows:

Intake:	1,704 ml.	3,408 ml.	3,920 ml.
Output:	936 ml.	3,860 ml.	3,630 ml.

18.8.56. *Labour.* The membranes ruptured spontaneously half an hour after the snuff was resumed and uterine contractions began one hour later. Vaginal examination revealed the cervix to be two fingers-breadth dilated, the breech was in the right sacro-lateral position and there was no prolapse of the umbilical cord.

Initially uterine function was of poor quality until about 10 hours after the membranes had ruptured when contractions became strong and painful, occurring every 3 minutes. Morphia, ¼ gr., was given with good effect and the labour progressed well for a further 6 hours when the contractions again became of poor quality, occurring every 10 to 15 minutes.

Vaginal examination after the labour had progressed for 19 hours revealed that the breech remained at the brim of the pelvis and the cervix was now half dilated.

The fluid balance during the labour was satisfactory and the patient was again due the daily dose of snuff after the inhalation of which the contractions improved for 2 hours and vaginal examination revealed that the cervix was now half dilated. Arrangements were now made to decompose the breech and bring down a leg in order to encourage more effective uterine contractions. Following the administration of the premedication (atropine sulphate, 1/100th gr. intravenously) the patient had an epileptiform convulsion. The blood pressure was 120/70, the urine was free from albumin and there was no evidence of oedema. Nevertheless tribromethanol, 6 ml. in 230 ml. of warm

tap water, was given rectally and shortly afterwards general anaesthesia was induced with a mixture of gas, oxygen and ether.

The findings at the last vaginal examination were confirmed and the flexed leg was brought down easily. The other leg was flexed by Pinard's manœuvre and brought down also and, the cervix being now fully dilated, the child was delivered by breech extraction, forceps being used to deliver the aftercoming head. The child, a male, weighed 7 pounds 3 ounces (3,266 g.). The placenta and membranes were expressed and the total blood loss was less than half a pint.

The patient recovered quickly from the sedation and showed no sign of pre-eclampsia. She did not wish to breast feed and therefore lactation was suppressed by stilboestrol 10 mg. thrice daily for 3 days. An X-ray of the chest showed no alteration in the size of the hilar shadows. The puerperium was uneventful and the patient was discharged on the 10th day.

Comment

Diabetes insipidus results from a deficiency of the posterior pituitary anti-diuretic hormone which in this case followed the onset of sarcoidosis. The diagnosis had been established before the beginning of the pregnancy and therefore the differentiation between diabetes insipidus and psychogenic polydypsia was not necessary (Carfagno *et al.*, 1953).

McLaren and McLeod (1942) described a case developing diabetes insipidus during pregnancy and improving spontaneously after delivery and in a review of the literature they found that in some instances the condition occurred only during pregnancy while in others there was improvement during pregnancy with recurrence in the puerperium. In the former type of case it was suggested that the anterior pituitary produced an excess of a diuretic hormone during the pregnancy and return to normal after delivery, restoring the balance with the inadequate anti-diuretic hormone of the posterior pituitary. But this theory was opposed by the case reported by Duvoir (quoted by McLaren and McLeod, 1942) which improved during pregnancy.

In the case now described there was no alteration in the diabetes insipidus since, when the Di-sipidin was stopped during the latter weeks of the pregnancy, the symptoms recurred. The painful uterine contractions which followed the inhalation of the snuff were in all probability due to a small amount of the oxytocic factor present in the preparation and this may well have been sufficient to expedite the onset of labour. It is difficult to ascribe the uterine inertia which was present to a deficiency of posterior pituitary hormone but the uterine contractions improved during labour with the Di-sipidin suggesting a partial deficiency of the oxytocic factor.

Fisher, Magoun and Ransom (1939) showed that destruction of the hypothalamic-pituitary nerve tracts in cats caused prolonged labour and, although reservation is made in applying the results of animal experiments to humans, it may be suggested that the inertia was caused in part by the deficiency of oxytocin. Marañón (1947) reported a case observed over 4 pregnancies and inertia occurred in 3, of which 2 resulted in stillbirths and the other was assisted by pituitrin injections with a successful conclusion. The fourth pregnancy ended with a miscarriage. On the other hand Dandy (1940) maintains that transection of the stalk of the hypophysis cerebri has no effect on pregnancy or delivery.

The cause of the fit during labour is not known as there was no evidence of pre-eclampsia nor history of epilepsy nor any evidence of cerebral sarcoidosis, though there may be some relation to the intravenous injection of atropine.

As shown by Donaldson and others (1951) the sarcoidosis had no effect on the pregnancy nor did the pregnancy cause any alteration in the progress of the sarcoidosis.

Summary

A case of diabetes insipidus complicating pregnancy is described where the condition had no effect on the pregnancy apart from a possible oxytocic effect resulting from the inhalation of the snuff. Some degree of inertia occurred during labour and posterior pituitary hormone deficiency is postulated as a possible cause.

Acknowledgments

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PREGNANCY ASSOCIATED WITH DIABETIC NEPHROPATHY

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ALTHOUGH pregnancy in diabetic women is now common, it is rare in obstetric practice to see patients with pregnancy and diabetic nephropathy. According to Root (1952) this condition takes first place as a cause of death in young patients, after 15 to 20 years of diabetes. The typical story is that a child develops diabetes in the early 'teens and this is brought under control with diet and insulin. Gradually the management of the diabetes becomes less thorough, especially after leaving school, and episodes of ketosis or coma occur. After 10 or 15 years like this the patient is found to have albuminuria, which is intermittent at first, but becomes constant in the next year or two. Hypertension develops and oedema occurs occasionally. Casts are found in the urine, and in the optic fundi haemorrhages and micro-aneurysms develop. Renal insufficiency progresses to death from uraemia in a few years. Post-mortem examination reveals sclerosis of the kidneys, with thick hyaline deposits in the centre of the glomeruli and in the renal arterioles. These hyaline deposits are very rare in non-diabetic nephritis and it is believed that the hyaline material is identical with that found in the islets of Langerhans.

The patient whose record is reported here appears to be a typical case of this condition. At the time of her recent pregnancy she was 26 years of age and she had suffered from diabetes since the age of 14. The onset of renal damage was suspected when she was 18, as she had slight albuminuria on many occasions with occasional granular casts in her urine, and a blood pressure of 145/100 mm. Hg was recorded once. A urea clearance test then showed the clearance to be 68 per cent of normal. At 22 years of age she developed diabetic coma from which she recovered after treatment in hospital. Routine examination at that time revealed that she had a cough with sputum positive for tubercle bacilli, and X-rays showed a lesion at the apex of the right lung. She was treated in a sanatorium with bed rest and Streptomycin followed by artificial pneumothorax for 3 years, after which time the lung disease appeared quiescent.

She was married in 1950, and after her discharge from the sanatorium she was very anxious to have a child. The chest physician was satisfied that the tuberculosis was not a contra-indication to pregnancy, but the diabetic physician advised against it in view of the evidence of renal damage. Professor Tunbridge was asked to give his opinion regarding the risk of pregnancy and he considered it inadvisable for three reasons: (1) The pregnancy would put a strain on her and might precipitate further renal damage. (2) The prognosis for duration of life was not good, perhaps 10 to 15 years. (3) She had proved a difficult diabetic to control. He forecast that her chances of getting a live child were less than normal, and the risk of her developing toxaemia of pregnancy was greater than normal.

The patient was warned of these dangers, but her desire for a child was very strong, and she became pregnant in the autumn of 1955. This pregnancy ended in a 3-months miscarriage in December, 1955. After the miscarriage her diabetes was satisfactorily controlled as judged on routine visits to the diabetic clinic.

In 1956 she became pregnant again, the last menstrual period being 16th June. In the early weeks there was some doubt regarding the diagnosis of pregnancy, but in October this was beyond doubt and she was admitted to the Diabetic Annexe at Pinderfields Hospital for

observation. On admission the blood pressure was 130/90 mm. Hg but there was no cardiac enlargement. There was a trace of albumin in the urine, and a few red cells were seen on microscopical examination. She was kept in hospital for 3 weeks, and during this time evidence of very early retinitis first appeared in the form of a few very small micro-aneurysms. However, the blood pressure settled to normal, and the albuminuria was never sufficient to be recorded by Esbach's method. She was receiving a diet of 1,400 calories with a daily injection of 32 units of soluble insulin, and 28 units of protamine zinc insulin. On this regime, the control was not satisfactory, there being numerous hypoglycaemic attacks. The diet was therefore increased to 2,300 calories with 32 units of soluble insulin before breakfast, and 24 units of Neutral Protein Insulin (Hagedorn) before the evening meal. This gave satisfactory control, and she was discharged on this regime at the 22nd week of pregnancy.

At 25 weeks she was seen in the antenatal clinic and the blood pressure was 160/90 mm. Hg. The urine contained 0·27 g. per cent albumin. She was admitted to the antenatal ward, and remained in hospital until her delivery. Her blood urea was 67 milligrams per cent. During the succeeding weeks her blood pressure fluctuated between 120/80 and 140/100 mm. Hg and the albuminuria ranged from 0·08 g. per cent to 0·35 g. per cent, being generally between 0·1 g. per cent and 0·2 g. per cent. Her diabetes was difficult to control so that she had hypoglycaemic attacks, and other episodes of hyperglycaemia in which the fasting blood sugar was as high as 313 milligrams per cent.

At 28 weeks her uterus corresponded with the duration of amenorrhoea, but at 31 weeks it was noticed that there had been no apparent growth of the foetus in the previous 3 weeks, and it was decided to give oestrogens in the hope of improving the uterine blood flow. Stilboestrol 10 milligrams t.i.d., was given by mouth, but there was little benefit from this treatment. From this time only very slight growth of the foetus took place.

Although the diabetes was kept under fairly satisfactory control by frequent adjustment of the insulin dosage, minute retinal haemorrhages became visible at 34 weeks, and the blood urea rose to 75 milligrams per cent by this time. It was feared that continuation of the pregnancy would probably lead to intra-uterine death of the foetus, besides aggravating the mother's condition, so it was decided to terminate the pregnancy as soon as the patient had reached 35 weeks, even though the foetus was obviously very small. It was felt that the grounds given by Professor Tunbridge for advising against pregnancy had been confirmed by the course of this pregnancy, and that a further pregnancy would carry a big risk to the mother. Our difficulties were explained to both parents, who were advised to permit sterilization at the time of operation. The husband readily consented to this course and, the patient herself agreed after much hesitation.

For 2 days before the operation her morning insulin and breakfast were delayed one hour, and on the day of the operation no insulin or glucose were given until the child had been delivered. The operation was performed under general anaesthesia, with thiopentone and nitrous oxide and oxygen, supplemented with relaxant drugs. The infant weighed only 2 pounds 13 ounces but she was vigorous and her appearance was far more mature than usual for such a small child. The usual technique for lower segment Caesarean section was followed and sterilization was performed by Irving's method. The placenta contained many infarcts.

The mother made a good recovery and her insulin requirements diminished. When she was discharged home the blood pressure was normal but the urine still contained a trace of albumin and the retinitis had progressed very slightly.

When seen at the postnatal clinic her blood pressure was 150/100 mm. Hg and her urine contained 0·52 g. per cent albumin. The retinitis was still present.

The infant made good progress and was discharged home at 7½ weeks when she weighed 5 pounds 5 ounces. She was artificially fed.

I have not found many references in the literature to this condition. In a series of 702 pregnant diabetics reported by Priscilla White (1952) there were 14 cases with renal disease. In 2 cases renal disease first appeared during the pregnancy. Of the 12 cases with previous renal

disease the condition progressed during pregnancy in 4 cases. Only 50 per cent obtained a live child. Clayton (1956) reported a series of 201 pregnancies in 176 diabetic patients. Five cases had renal disease, probably diabetic nephropathy, and in 4 the pregnancy was terminated. The fifth patient became extremely ill about the thirtieth week with increasing hypertension and gross generalized oedema, and she nearly lost her life from pulmonary oedema before the pregnancy was terminated.

Priscilla White remarks that from 1922–1940 juvenile diabetics still died from coma or sepsis, but since 1940 young diabetics have lived to become pregnant and to develop vascular disease, including diabetic nephropathy. It is therefore likely that the number of these cases will increase as time goes on, and they will obviously present a very difficult problem to the obstetrician as well as to the physician.

I am grateful to Mr. D. W. Currie and Dr. R. G. Paley for permission to report this case.

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PROLONGED PYREXIA DUE TO SUPPURATION AND ABSCESS FORMATION IN UTERINE FIBROIDS

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INFECTION with abscess formation is an unusual complication of interstitial uterine fibroids. The following case is of interest in view of the absence of local pain or tenderness, which might have suggested this diagnosis, in a patient undergoing investigation of obscure pyrexia.

CASE REPORT

Mrs. H., aged 54, had been in good health until 20th August, 1955 when she was taken ill with rigors, headache, malaise and nocturnal sweats, with a swinging temperature rising at times to 103° F. (39·5° C.). As no simple cause could be found for the fever she was admitted to her local hospital after five days.

At that time, apart from the raised temperature and pulse rate, the only abnormality to be found was in the abdomen, where the uterus was felt to be enlarged to the level of the umbilicus with fibroids. There was no abdominal pain or vomiting and no tenderness or guarding on palpation.

She gave a history of 2 normal pregnancies, and was still menstruating regularly, her periods lasting for 7 days every 4 weeks. These had been heavier recently with passage of clots, but no dysmenorrhoea. A curettage had been performed in 1945 on account of blood-stained intermenstrual discharge, which had not recurred. There was nothing else relevant in her past history.

During the next few days the following investigations were undertaken with these results:

Blood. The haemoglobin was 85 per cent (12·6 g./100 ml.), the white cell count was normal, and the erythrocyte sedimentation rate 79 mm. in one hour (Westergren). A pure culture of *Bacterium coli* was isolated from the blood on two occasions. It was sterile on three occasions.

Agglutinations. Negative to Salmonella Typhi "H" and "O", Paratyphi A and B, Proteus OXK, OX19 and OX2 and *Brucella abortus.* The Paul Bunnell test was negative.

Urine. There were no casts, no pus cells and culture was sterile.

Throat swab. There were normal commensals only.

Faeces. No pathogens were cultured.

X-ray examination. The chest film was normal. The intravenous pyelogram was normal.

For 3 weeks she continued to have a high swinging temperature, rising at times to 104° F. (40° C.), with occasional rigors, but no new symptoms or signs developed.

On 18th September, 1955 she was transferred to the Middlesex Hospital for further investigation. On admission she was obese and looked healthy though rather pale. The heart and lungs were normal and the blood pressure 160/95 mm. Hg.

All the routine laboratory investigations were repeated with negative results, but during the subsequent 3 weeks the total white cell count rose to 20,000 per c.mm. with 90 per cent neutrophils, and the erythrocyte sedimentation rate rose to 140 mm. in one hour (Westergren).

The haemoglobin level fell to 63 per cent (9·2 g. per 100 ml.) with normochromia. No malarial parasites were seen in blood smears.

X-ray examinations of the chest, sinuses, and teeth were normal. All liver function tests were normal, and four blood cultures were sterile, with no further culture of *Bact. coli*. The serum proteins were 6·1 g. per 100 ml. (albumin 3·8 g. and globulin 2·3 g.). The electrophoretic pattern showed a grossly raised $\alpha 2$ globulin, with the comment: "In view of the polymorphonuclear leucocytosis and raised sedimentation rate, this does not appear to be diagnostic of any particular pathology, although this could be due to malignant disease."

A course of penicillin (500,000 units 6-hourly) was given for four days, but had no effect on the temperature.

At this stage, in spite of the absence of symptoms, a gynaecological opinion was obtained concerning a possible cause for the continued pyrexia, then in its sixth week. At this examination the presence of a large abdominopelvic mass was confirmed, but there was still no pain or tenderness on palpation. The most likely diagnosis seemed to be pyosalpinx associated with uterine fibroids, or a malignant ovarian tumour with necrosis and infection. Other medical and surgical causes seemed to have been eliminated by the earlier investigations.

A blood transfusion was given to correct anaemia before operation. On 3rd October, 1955, under general anaesthesia, a vaginal examination was made before opening the abdomen. Apart from the uterine fibroids there was no abnormality to be found, both vagina and cervix appearing healthy.

Laparotomy was performed, confirming the diagnosis of fibroids. Both Fallopian tubes and ovaries appeared normal, and there were no adhesions in the pelvis or indications of any previous inflammation. There was no free fluid, and no other abnormality could be found in the peritoneal cavity. In view of the size of the uterus and the patient's age and history of menorrhagia, total hysterectomy with bilateral salpingo-oöphorectomy was performed.

There appeared to be no abnormal pelvic congestion, haemostasis was satisfactory, and as no discharge escaped from the cervix there was no contamination of the field of operation.

On opening the uterus afterwards, some six fluid ounces (170 ml.) of thick, greenish-yellow, pus escaped from a cavity in the centre of a necrotic fibroid. This was approximately 3 inches (7·5 cm.) in diameter, and was mainly interstitial, though it encroached on the uterine cavity over part of its surface. Smaller adjacent fibroids appeared to be similarly sloughing and purulent, though there was no pus in the uterine cavity proper. A swab taken at the time was mislaid, so no culture was obtained.

One pint of blood was given during operation, and the patient was returned to the ward in good condition.

The post-operative progress was satisfactory. The temperature, which had previously been ranging up to 101°–102° F. (38·4°–38·9° C.), fell at once to normal limits, and did not rise above 99°F. (37·2°C.) during her convalescence.

A course of penicillin (500,000 units b.d.) was given from the time of operation for 5 days. Microscopical section confirmed the diagnosis of necrotic and infected fibroids with no other significant abnormality in the uterus and adnexae.

The wound remained clean and healed satisfactorily, and the white cell count fell to normal limits, being 8,400 per c.mm. on the tenth day after operation, with erythrocyte sedimentation rate of 70 mm. in one hour. On the fifteenth day the sedimentation rate was 60 mm. in one hour with haemoglobin 75 per cent (11·1 g. per 100 ml.).

The patient was discharged fit on the eighteenth post-operative day. When seen in the out-patient department some 4 months after operation the haemoglobin was 85 per cent (12·6 g. per 100 ml.) and she remained well, so she was discharged from the clinic.

Discussion

Abscess formation of this type in a uterine fibroid is rare, and must be a most unusual cause of prolonged pyrexia. Of interest too in this case was the absence of any abdominal or pelvic pain. It was fortunate that the pus was so located that the abscess was removed *in toto*, with no soiling of the peritoneal cavity.

In this case, had a curettage been performed first, the abscess cavity might have been opened up, necessitating a staged procedure with preliminary drainage *per vaginam*.

While infection, suppuration, and sloughing are not uncommon complications of submucous polypoid fibroids, especially after puerperal infection or curettage, most authors are agreed on the rarity of abscess formation in interstitial tumours.

The problem is summed up well by Novak (1952) who states: "The type of myoma most prone to infection is the submucous, because it offers such obvious portals of entry to infectious organisms from the genital tract. The overlying mucosa is characteristically thinned out, and almost invariably its infection is evident in the inflammatory changes seen microscopically. The mucosa may be lost over considerable areas through ulceration, and the infectious process may penetrate deeply into the substance of the myoma.

"Suppuration may occur, and in rare instances abscesses have been noted in the substance of the tumour. Such infectious processes may have their inception in such operations as uterine curettage, and they are prone also to develop after miscarriage or parturition in uteri containing myomas of this submucous variety.

"When infection is of virulent type extensive sloughing of the tumour may occur, with evidence of general sepsis. Subserous and interstitial tumours are less frequently infected than the submucous variety. The former however may be involved in inflammatory diseases of the adnexa, the tumours showing marked inflammatory changes which begin on the peritoneal surface and penetrate the tumour to a varying degree."

Although infection usually enters via the uterine cavity, on rare occasions it appears to be blood borne. Thus Shaw (1952) states: "Haematogenous infections of myomata arise from time to time as the results of general infections with streptococci, staphylococci and the bacillus coli . . . As a result simple or multiple abscesses form in the tumour and cause local pain and tenderness. Metastatic abscesses of this kind are extremely rare at the present day."

In this case no other focus of infection could be found. While the causative organism was never established with certainty, it is of interest that on 2 out of 7 occasions a positive blood culture of *Bact. coli* was obtained.

Summary

(1) A case is described where obscure pyrexia of six weeks duration was due to abscess formation in a uterine fibroid.

(2) Although this is an uncommon condition it is still more remarkable that there were no local symptoms or physical signs pointing to the site of infection.

(3) Attention was eventually focussed on the pelvic organs by a process of elimination, after other causes of prolonged pyrexia had been excluded.

(4) In spite of thorough investigation and modern aids to diagnosis, an exploratory laparotomy was necessary before the correct diagnosis could be established.

We wish to thank Dr. A. Willcox and Mr. Ian Jackson for permission to publish this case, and the Bland-Sutton Institute of Pathology and the Courtauld Institute of Biochemistry for the investigations performed.

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THE BARTHOLIN FAMILY

BY

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DURING a review of the aetiology of inflammation and cysts of Bartholin's glands, interest was aroused in the discoverer of these glands. This led to a search of the literature and the tracing out of the history of a remarkable family of Danes, who flourished in the 17th and 18th centuries.

The first of the line of medical interest was Caspar Bartholinus who lived from 1585 to 1629. He was born at Malmo in Sweden and was extremely precocious. He could read at the age of 3 and by the time he was 13 he was composing Greek and Latin verse and delivering public orations in those tongues. He studied at Copenhagen, Rostock and Wittenberg. Underwood (1950) states that by the age of 26 he had refused chairs of philosophy, anatomy and Greek, but Singer (1925) says he was professor of philosophy at Basel, of anatomy at Naples and of Greek at Montpellier. Whichever of these versions is accepted it seems that Caspar Primus would have been a notable man in any age. Singer's version of the activities of Caspar Bartholinus shows that he travelled widely and visited Germany, the Netherlands, Britain and France, as well as Switzerland and Italy.

When he was in Italy he studied under Fabricius ab Aquapendente (1533–1619) who was professor of anatomy at the University of Padua, which played an important part in the Renaissance of Medicine. Fabricius was one of the successors of the anatomist Andreas Vesalius (1514–1564), who has been described as the founder of modern anatomy. Other pupils of Fabricius were William Harvey (1578–1657) and Olaus Wormius (1588–1654). One is tempted to suggest that Caspar Bartholinus must have met William Harvey before the latter's discovery of the circulation of the blood. He might have met him in Padua or in Britain, but there is no evidence to support such a speculation.

Olaus Wormius was a contemporary of Bartholinus, and he practised in London before finally settling in Copenhagen. It was he who described the bones which may occur within the sutures of the skull, and it was Caspar Bartholin who suggested they should be called Wormian bones. The uncharitable may feel that this was very much a family affair since Bartholinus and Wormius were brothers-in-law, Bartholin having married Anna Fincke and Worms having married her sister. There may even be more to it than this, because in the National Medical Library at Washington is a book by the son of Bartholin which carried the portraits of Fuirenius, Olaus Wormius, Thomas Fincke, Caspar Bartholin, Sim. Paulli and Joh. Rhodius. The book is a history of anatomy at Copenhagen and one wonders if the Thos. Fincke mentioned was the father of the wives of Bartholin and Worms.

In 1610, at the age of 25, Caspar Bartholinus took his degree of Doctor of Medicine. Three years later he became professor of medicine at Copenhagen, and he held this chair till 1624. In that year he suffered a serious illness, the nature of which is not known, and vowed that if he recovered he would devote himself to divinity. He did recover and with apparently characteristic brilliance he became canon of Roskilde and professor of theology at Copenhagen. This chair he held until his death in 1629 at Soro in Zeeland.

There are at least nine papers published by Caspar Bartholin, mentioned in the Surgeon-General's catalogue. During his lifetime they were published in Wittenberg, Copenhagen and Frankfurt and after his death one was published

in Paris and one in Cambridge. The subjects of his papers were anatomy, medicine, surgery, astrology, philosophy and metaphysics.

Caspar Bartholinus had four children of whom Thomas, the second son, is of the most medical interest. The other sons were Jacob (d. 1653) an orientalist, Erasmus (1625–1698) a physicist, and Albert a biographer. Thomas was born in 1616 at Copenhagen and died at Haagestaed in 1680. He travelled for nine years to foreign universities but the main influence upon him was Dutch. He was a contemporary, at Amsterdam, of Regnio de Graaf, who first discovered the Graafian follicle of the ovary.

He was a supporter of William Harvey and among his papers are several references to the circulation of the blood. Extracts from these read "observationibus tertiam ad sanguinis circulationem reformata", "ad circulationem Harveianam", and "Gulielmi Harvei de venis lactis sententia expensa ab eodem Th. Bartholino". One of his books was published in England and its title was *Bartholinus anatomy: made from the precepts of his father, and from the observations of all modern anatomists, together with his own. In four books and four manuals answering the said books . . . Also two epistles of the circulation of the blood. Published by Nich. Culpepper and Abdiah Cole, London. J. Streater 1668.*

Perhaps his interest in the circulation was stimulated by his father, who had first learned of the valves in veins from Fabricius, who was also Harvey's teacher.

Thomas Bartholin first described the thoracic duct in man, though it had been earlier described in animals by Pecquet (1622–1674), and he gave the first full description of the whole lymphatic system in man. Also credited to him are Bartholin's *anus, i.e. the aditus ad aqueductus cerebri*, and Bartholin's duct, which is the longer and larger of the sublingual ducts, though it is probable that his son described the latter.

He became professor of mathematics at Copenhagen in 1646 and two years later moved to the chair of anatomy. He retired from this post in 1661 and went to live the life of a landed gentleman at Hagestaed House, not far from Copenhagen. Unfortunately, fire broke out at his house and destroyed many manuscripts and the library. He therefore returned to Copenhagen where he became the university librarian and physician to King Christian V, a somewhat odd mixture of occupations in our eyes. He died in 1680.

There are 38 publications listed against his name in the Surgeon-General's Catalogue. Papers about him deal with his activities as a poet, nobleman and landed proprietor. He must have been a most remarkable man.

Thomas Bartholin had five sons and one daughter, the latter, Margaret, being a poetess. The eldest son was Caspar Bartholinus or Caspar Secundus (1655–1738). He was born in Copenhagen and like his father and grandfather he travelled much abroad. His main centres of education were probably Paris, where he came under the influence of Duverney, and Amsterdam where he was a pupil of Ruysch and Swammerdam.

Jan Swammerdam (1637–1680) was an interesting man who probably had some influence on Caspar Secundus. He had been intended for the Church, but took up medicine instead. His father then withdrew all his support and Swammerdam had some financial difficulty. Later he turned to entomology. He developed a technique for injection of blood vessels, which showed them up prominently. When he became an entomologist he gave the secret of his method to Ruysch, who ultimately became professor of anatomy and botany at Amsterdam. Ruysch wrote on the mechanics of childbirth.

Swammerdam obtained his doctorate of medicine at the University of Leyden with a thesis on respiration. He was the first to show that the unaerated lung of a stillborn infant sank in water, an observation still of importance today. In 1701, thirty or more years after this thesis was written, Caspar Secundus wrote a paper called "De respiratione animalium".

In 1672 Swammerdam published a work on the human uterus and this was the year in which de Graaf discovered the ovarian follicle. At this time Caspar Secundus was 17 years old. Only 5 years later he published his paper which described the vestibulovaginal glands for the first time. It seems likely that Caspar's interest in the anatomy of the female genitalia was a direct result of coming under the influence of Ruysch, Swammerdam and de Graaf.

Joseph Guichard Duverney (1648–1730) was professor of anatomy at Paris, and there is no doubt that Caspar Secundus was taught by him. As Duverney had described the vestibulo-vaginal glands in cattle, it may be that this prompted Bartholin to look for them in woman. Bartholin's paper describing these glands was entitled "*De ovarii mulierum et generationis historia, epistola anatomica, antea Romae edita; cui jam accessit alia ejusdem argumenti*". It was published in 1678 in Amsterdam.

Until the time of Caspar Secundus and Swammerdam it was thought that the ovaries secreted a seminal fluid which was increased in amount by sexual stimulation. Swammerdam maintained that the discharge did not come from the ovaries and Bartholin showed that it came from the uterus and vagina.

Later in life Caspar Secundus busied himself in politics and public administration in Copenhagen. He died there in 1738.

The Renaissance of Learning is a hard period to define, because there was no revolutionary change in habits of thought, but only a slow evolution of a new method and approach to learning of all kinds. An oversimplified view, but one with a grain of truth, is that there was a change of emphasis from the deductive method to that of induction, empiricism and pragmatism. In the van of this new approach were the universities of Salerno, Montpellier, Bologna and Padua and from the last three of these Caspar Primus was one of the men who carried the new learning northwards from the Mediterranean.

Thomas Bartholin and Caspar Secundus restricted their educational journeyings to Northern Europe, thus showing that the Renaissance had established itself there, in medicine at least, shortly after the time of Caspar Primus.

This brief study also shows that even three centuries ago discoveries were rarely made by one man working in isolation, and that any man depends for his inspiration on the climate of thought in which he finds himself. Thus, Caspar Secundus, whose father and grandfather had been anatomists of repute, found in both Amsterdam and Paris that attention was being directed to the problems of the female genitalia, and in particular to the problem of the origin of female semen. With his interest drawn to this area of anatomy he used the teachings of Duverney, Ruysch, Swammerdam and de Graaf and applied the empirical new approach which was a product of the Renaissance. This new approach had been learned by his grandfather, who had helped to bring its methods northwards from its native Italy.

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OBSTETRICAL-GYNAECOLOGICAL EPONYMS: JAMES YOUNG SIMPSON AND HIS OBSTETRIC FORCEPS

BY

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THE obstetric forceps has been modified and redesigned in new form probably more times than any of the other countless number of instruments and devices that man's mind has conjured up for the diagnosis and treatment of his ills. The Chamberlen family is often credited with invention of the first safe and effective forceps, in the late sixteenth or early seventeenth century; but archaeological evidence (Fig. 1) shows the forceps to have been in use for the delivery of living infants much earlier, probably the second or third century, in the days of the Roman Empire (Baglioni, 1937). During the latter part of the nineteenth century almost every obstetrician of renown seems to have felt the need to add his own modification to the forceps; and even now scarcely a year passes without the addition of at least one new instrument to our forceps arsenal. For fully a century now, however, year in and year out, the vast majority of forceps deliveries has been carried out by means of an instrument popularized by Sir James Young Simpson and usually known as the Simpson forceps, although models embodying minor changes continue to bear the names of their new inventors.

Simpson demonstrated his forceps for the first time on 10th May, 1848 at a meeting of the Edinburgh Obstetrical Society (Simpson, 1848). "They differ from the short forceps in some points of construction," he explained, "but more particularly in regard to their mode of application and working. They differ for example in their length; in the shanks being parallel for some distance beyond the lock, an indispensable point in order to prevent them injuring the outlet; in their blades being curved; and in the part intended to embrace the head being sufficiently long and large . . . The blades are the same as Dr. F. Ramsbotham's, but scarcely so much curved. The lock is Smellie's, but with knees or projections above it of such size as to prevent the blades readily unlocking in the intervals between the pains, these giving it the fixed character of the locks of Levret and Bunninghausen's instruments, without their complexity. The joints are made so loose as to allow of their lateral motion and overlapping to a very considerable degree, thus facilitating their introduction and application. And, lastly, the handle is that used by Naegele and other German accoucheurs, viz., with transverse knees or rests below the lock for one or two of the first fingers of the right hand to drag by, the long forceps being only properly used as an instrument of traction, not of compression. In addition, the handles are grooved and marked on the anterior side, to distinguish that from the other side when the blades are within the pelvis . . ."

The forceps were used in the management of uterine inertia, haemorrhage during labour, and other complications, "but the common reason for employment of the long forceps," in Simpson's words, "is morbid contraction of the brim of the pelvis in its most general form, and from its most general cause, viz., in the conjugate or antero-posterior diameter, from projecting forward of the promontory of the sacrum. How are the long forceps applied when used in this, the case in which they are most generally had recourse to in practice? It is first requisite to state, that under this complication the child's head is found situated in the brim, with its long or fronto-occipital diameter lying in the transverse diameter of the brim, or with the forehead looking to one ilium, and the occiput looking to the other. In other words, the long diameter of the head is not placed, as usual, in the right

diagonal diameter of the brim, but more in its transverse; for where the promontory of the sacrum forms a morbid projection, the transverse forms the longest diameter of the brim, and, consequently, the one in which the child's head comes to be placed by the uterine efforts . . . the lateral surfaces of the child's head come to be compressed between the protruding sacral promontory and the interior of the symphysis pubis . . ."

Modern obstetrical teaching emphasizes the importance of symmetric, or cephalic, application of the forceps to the sides of the foetal head. Simpson, by contrast, advised asymmetric, or pelvic, application of the blades. "The blades of the long forceps," he wrote, "should be placed obliquely upon the child's head—one, the posterior, over the side of the occiput; and the other, or anterior, over the side of the brow or temple, and consequently should be situated in the oblique diameter of the brim. (See Woodcut, Fig. 3.)—The markings on the child's head after birth always show this mode of application of the instrument: when properly applied upon the mother, and when their situation relative to the pelvis is examined, they are found to have assumed this position; and in experiments with the instrument (when the head of a dead child is fixed in a pelvis with a contracted brim), this is the position and relation which the instrument will be seen to assume with relation to the infantile head and maternal pelvis. Besides, in thus placing the instrument, while we incur less danger of injuring the urethra and other important parts, we place the blades of the instrument in exactly those parts of the pelvic circle where there is least pressure and consequently most room for them . . ."

Simpson is remembered eponymically for his forceps, but far greater to his credit was his introduction of anaesthesia into obstetrical practice. On 19th January, 1847, for the first time, he administered ether to a patient in labour, reporting the case in the March issue of the *Monthly Journal of Medical Science* (Simpson, 1847a). "The pelvis of the mother", Simpson wrote, "was greatly contracted in its conjugate diameter from the projection forwards and downwards of the promontory of the sacrum; the lumbar portion of the spine was distorted; and she walked very lamely. The present was her second confinement. Her first labour had been long and difficult . . . delivered by craniotomy . . . Even after the cranium had been fully broken down, a considerable time and much traction had been required to drag the diminished and mutilated head of the infant through the contracted brim of the pelvis; and she was long in recovering. Contrary to the urgent advice of her medical attendant, Mr. Figg, he was not made aware of her present or second pregnancy till she had arrived at nearly the end of the ninth month. It was thus too late to have recourse to the induction of premature labour, which had been strongly pressed upon her as the only means of saving her child, should she again fall in the family way. The pains of her second labour commenced in the forenoon of the 19th. I saw her with Mr. Figg at five o'clock in the afternoon, and again at seven. The os uteri was pretty well dilated, the liquor amnii not evacuated, the presenting head very high, mobile, and difficult to touch; and a pulsating loop of the umbilical cord was felt floating below it in the unruptured bag of membranes. From five to nine o'clock the pains seemed only to push the circle of the os uteri further downwards, without increasing its dilatation, or making the head in any degree enter into the pelvic brim. Assisted by Dr. Ziegler, Dr. Keith, and Mr. Figg, I shortly after nine o'clock made the patient inhale the ether vapour. As she afterwards informed us, she almost immediately came under the anodyne influence of the ether. But in consequence of doubts upon this point, its use was continued for nearly twenty minutes before I proceeded to turn the infant (as I had previously predetermined to do). A knee was easily seized, and the child's extremities and trunk readily drawn down; but extreme exertion was required in order to extract the head. At length it passed the contracted brim with the anterior part of its right parietal bone deeply indented by pressure against the projecting promontory of the sacrum, and the whole cranium flattened and compressed laterally. The infant gasped several times, but full respiration could not be established . . .

"On questioning the patient after her delivery, she declared that she was quite unconscious of pain during the whole period of the turning and extracting of the infant, or indeed from the first minute or two after she first commenced to breathe the ether. The inhalation was discontinued towards the latter part of the process, and her first recollections on awaking were 'hearing', but not 'feeling', the head of the infant 'jerk' from her (to use her own expressions), and subsequently she became more roused by the noise caused by the preparation of a bath for the child. She quickly regained full consciousness, and talked with gratitude and wonderment of her delivery, and her insensibility to the pains of it . . ."

The ensuing controversy over the use of anaesthesia in obstetrics has had few equals in the annals of medicine. Simpson's practices were violently opposed by many of the clergy as well as his medical peers, but to each attack the articulate Simpson replied with devastating logic, impeccable taste, albeit liberally salted at times with incisive sarcasm, and extensive biblical quotations in rebuttal of his critics' protestations against man's alleviation of the travail of childbirth (Simpson, 1856). The distinguished Meigs of Philadelphia referred to the pain of parturition as a "physiological pain", and the equally renowned Ashwell of London wrote in the *Lancet* (Ashwell, 1848) that to use anaesthesia in obstetrics constitutes "unnecessary interference with the providentially arranged process of healthy labour . . . sooner or later, to be followed by injurious and fatal consequences".

Recalling the words of Galen: *dolor dolentibus inutilis est* (pain is useless to the pained), Simpson went further, demonstrating the mortal potentialities of pain. By widespread questionnaire study of the results of thigh amputation he showed that ether anaesthesia had reduced the mortality from the operation by almost half. "Bodily pain," he wrote (Simpson, 1847b), "with all its concomitant fears and sickening horrors . . . is, with very few, if indeed any exceptions, morally and physically a mighty and unqualified evil. And, surely, any means by which its abolition could possibly be accomplished, with perfect security and safety, deserves to be joyfully and gratefully welcomed by medical science, as one of the most inestimable boons which man could confer upon his suffering fellow-mortals."

Arguing for the extension of anaesthesia to obstetrics, Simpson (1847a) made the forceful, impassioned plea: "Now, if experience betimes goes fully to prove to us the safety with which ether may, under proper precautions and management, be employed in the course of parturition, then . . . instead of determining . . . whether we shall be 'justified' in using this agent . . . it will become, on the other hand, necessary to determine whether on any grounds, moral or medical, a professional man could deem himself 'justified' in withholding, and *not* using any such safe means (as we at present presuppose this to be), provided he had the power by it of assuaging the agonies of the last stage of natural labour, and thus counteracting what Velpeau describes as 'those piercing cries, that agitation so lively, those excessive efforts, those inexpressible agonies, and those pains apparently intolerable', which accompany the termination of natural parturition in the human mother."

Simpson's entreaties were met at first by the reticence characteristic of his conservative colleagues, as evidenced by his address to the Medico-Chirurgical Society of Edinburgh on 1st December, 1847. "Probably at the date at which I write," he lamented, "there is not one in twenty—perhaps not one in a hundred—of the physicians and surgeons of Great Britain who have, as yet, thought seriously upon the propriety of alleviating and annulling the tortures attendant on human parturition; or who have acknowledged to their own minds the propriety of bestirring themselves so as to be able, in the exercise of their profession, to secure for their patients an immunity from the throes and agonies of childbirth."

It soon became apparent to Simpson that ether suffered from certain shortcomings as an obstetrical anaesthetic, and in the autumn of 1847 he began his search for a better agent, in collaboration with Drs. Thomas Keith and J. Matthews Duncan. Their experiments were carried out at the conclusion of the day's work, in Simpson's dining room. A small quantity of

FIG. 1

Ancient marble bas-relief depicting a birth scene. The accoucheur, in the centre, holds a pair of obstetric forceps aloft in his right hand. This marble tablet, measuring 74 × 55 cm., was discovered in the early twentieth century in the vicinity of Rome. The attire and furnishings in the scene date it in the second or third century A.D. (From Baglioni).

FIG. 2
James Young Simpson (1811–1870).

FIG. 3
Illustration from Simpson's paper, showing application of his forceps.

the test liquid was placed in a cup or drinking glass, which was immersed in hot water, if necessary, to increase the volatility. The experimenters then proceeded with their hazardous task of inhaling the vapours and noting the effects. It was in this manner that Simpson and his assistants came upon the anaesthetic properties of chloroform on 4th November, 1847.

Exhilarated by his new discovery, Simpson employed chloroform in the confinement of the wife of Dr. Carstairs of Edinburgh 4 days later, the child being named "Anaesthesia". Simpson reported the event to the Medico-Chirurgical Society of Edinburgh on 10th November, 1847 in the following words (Simpson, 1847c): "The lady to whom it was first exhibited during parturition had been previously delivered in the country by perforation of the head of the infant, after a labour of three days' duration. In this, her second confinement, pains supervened a fortnight before the full time. Three hours and a half after they commenced, and ere the first stage of the labour was completed, I placed her under the influence of the chloroform, by moistening, with half a teaspoonful of the liquid, a pocket handkerchief, rolled up into a funnel shape, and with the broad or open end of the funnel placed over her mouth and nostrils. In consequence of the evaporation of the fluid, it was once more renewed in about ten or twelve minutes. The child was expelled in about twenty-five minutes after the inhalation was begun. The mother subsequently remained longer soporose than commonly happens after ether. The squalling of the child did not, as usual, rouse her; and some minutes elapsed after the placenta was expelled, and after the child was removed by the nurse into another room, before the patient awoke. She then turned round and observed to me that she had 'enjoyed a very comfortable sleep, and indeed required it, as she was so tired but would now be more able for the work before her.' . . . In a little time she again remarked that she was afraid her 'sleep had stopped the pains'. Shortly afterwards, her infant was brought in by the nurse from the adjoining room, and it was a matter of no small difficulty to convince the astonished mother that the labour was entirely over, and that the child presented to her was really her 'own living baby'."

Three weeks later, at its meeting on 1st December, 1847, Simpson employed his most impassioned oratory in an address to the same Society. Singing again the praises of anaesthesia for childbirth, and especially of the newly-discovered merits of chloroform, he stated: "I do not remember a single patient to have taken it who has not afterwards declared her sincere gratitude for its employment, and her indubitable determination to have recourse again to similar means under similar circumstances. All who happened to have formerly entertained any dread respecting the inhalation, or its effects, have afterwards looked back, both amazed at, and amused with, their previous absurd fears and groundless terrors. Most, indeed, have subsequently set out, like zealous missionaries, to persuade other friends to avail themselves of the same measure of relief, in their hour of trial and travail . . . All of us, I most sincerely believe, are called upon to employ it by every principle of true humanity, as well as by every principle of true religion. Medical men may oppose for a time the super-induction of anaesthesia in parturition, but they will oppose it in vain; for certainly our patients themselves will force the use of it upon the profession. The whole question is, even now, one merely of time. It is not—Shall the practice come to be generally adopted? but, When shall it come to be generally adopted? Of course, it will meet from various quarters with all due and determinate opposition. Medical men will, no doubt, earnestly argue that their established medical opinions and medical practices should not be harshly interfered with by any violent innovations of doctrine regarding the non-necessity and non-propriety of maternal suffering. They will insist on mothers continuing to endure, in all their primitive intensity, all the agonies of childbirth, as a proper sacrifice to the conservatism of the doctrine of the desirability of pain. They will perhaps attempt to frighten their patients into the medical propriety of this sacrifice of their feelings; and some may be found who will unscrupulously ascribe to the new agency any misadventures, from any causes whatever, that may happen to occur in practice. But husbands will scarcely permit the sufferings of their wives to be perpetuated, merely in order that the tranquillity of this or that medical

dogma be not rudely disturbed. Women themselves will betimes rebel against enduring the usual tortures and miseries of childbirth, merely to subserve the caprice of their medical attendants. And I more than doubt if any physician is justified, on any grounds, medical or moral, in deliberately desiring and asking his patients to shriek and writhe on in their agonies for a few months or a few years longer—in order that, by doing so, they may defer to his professional apathy, or pander to his professional prejudices."

In 1853 John Snow, the first full-time physician anaesthetist, administered chloroform to Queen Victoria during the birth of Prince Leopold, her eighth child; and Her Majesty was lavish in her appreciation of the new agent and the pain relief it provided. This, probably more than any other single event, bowled over most of the remaining opposition to anaesthesia in labour and led to the rapid and widespread acceptance of chloroform in obstetrical practice. Not long thereafter Simpson was made a baronet, the inscription on his coat of arms reading "VICTO DOLORE" (pain conquered).

With his characteristic vision Simpson (1847b), after he introduced ether into obstetrics, foresaw the advantages of a special anaesthesia room for surgical patients, for in September, 1847 he wrote: "In our surgical hospitals, if a ward immediately adjoining the operating theatre were set aside for operation cases, it would in this way facilitate the process of etherization, and ensure more certain and perfect results from it."

James Young Simpson was born 7th June, 1811 in Bathgate, Scotland, the youngest of seven sons of the village baker (Anderson, 1911; Ballantyne, 1911; Barbour, 1911; Croom, 1911; Findley, 1939; Hart, 1911; Robinson, 1946; Simpson, A. R., 1911; Simpson, E. B., 1911; Watson, 1936, 1948). At age 14 he enrolled in the University of Edinburgh, with the help of his family's combined resources, but withdrew from the arts course two years later to pursue the medical curriculum. After three years of medical study, when Simpson had completed all the required courses, he passed his final examination and received the diploma of the Royal College of Surgeons. Being only 18 years old, however, he had to wait two more years for his licence to practise. During the interim he undertook further studies in midwifery, alternately assisted the professor of pathology at the university and Mr. Dawson, the family doctor in Bathgate, and visited the clinics of France and England. Simpson then returned to Edinburgh and entered general practice, but devoted his principal attention to midwifery. He soon obtained an appointment at the Lying-in Hospital and in 1838 began giving courses of lectures in midwifery on his own. When he was only 28 years old he became a candidate for the recently vacated chair of midwifery at the university, waging his campaign for this coveted position in a manner reminiscent of today's political contests. When his state of bachelorhood was mentioned in argument against his appointment, Simpson promptly took unto himself a wife. The Town Council finally elected him to the chair by a single vote's margin over his chief rival, Evory Kennedy, Master of the Rotunda in Dublin. Simpson's wife is said to have subsequently "poured out more tea than any woman in Scotland".

The lectures of the newly-elected professor attained a new high in popularity, surpassing in attendance all the other medical courses in the university. In addition to his forceps and his introduction of anaesthesia, Simpson made a number of other important contributions to obstetrics and gynaecology. He invented a cranioclast for fracturing the base of the foetal skull, and contrived the uterine sound and the sponge tent for dilating the cervix, thereby providing access to the uterine cavity for the removal of endometrial polyps. Almost at the same time as Semmelweis he called attention to the contagiousness of puerperal fever, giving the most convincing exposition until then of the similarity between this scourge and surgical fever; but he failed to encourage Lister, working contemporarily at the University of Edinburgh, in the latter's experiments on antisepsis, and never accepted Lister's concept of the bacterial origin of infection. He wrote on hermaphroditism and on the freemartin, and dispelled the widely held but erroneous belief that among human twins the female was sterile if her co-twin was a male. Simpson was probably the first to stress the importance of bimanual examination of gynaecological patients. "In making this

examination," he wrote in 1850, "as in making most other examinations of the uterus, a rule requires to be followed which is too often forgot, namely to use both hands for the purpose. For if we are examining the uterus internally with the forefinger, or fingers of the right hand, the facility and precision of this examination will be found to be immensely promoted by placing the left hand externally over the hypogastric region, so as to enable us by it to steady, or depress, or otherwise operate upon the fundus uteri. The external hand greatly assists the operations of that which is introduced internally; and farther we can generally measure, between them, the size, relation, &c., of the included uterus."

Simpson's interests ranged wide beyond the limits of his profession. He published extensively on archaeological subjects, became an ardent and authoritative antiquarian, and remained constantly engrossed in literature, philanthropical enterprises, medical reforms, and civil and university politics. He served as President of the Edinburgh Obstetrical Society from 1841 to 1858. His nephew and successor to the chair of midwifery in the university, Sir Alexander Simpson, later spoke of Simpson's house as "a rendezvous for all sorts and conditions of men. The strangest streams of life were constantly flowing through it. Candidates for seats in Parliament or in the Council Chamber of the city, for vacant chairs in the University, for posts in the Infirmary, for lectureships in many schools of medicine, and for pulpits in town or country—all came to seek his advice and bespeak his influence. Antiquaries came with their latest finds; artists and architects sought his opinion of their designs; poets brought him their new poems, and novelists their stories; the Arctic voyager, the African explorer, the traveller from Mecca, missionaries from all parts of heathendom, came with news and gifts of every kind." A companion who accompanied him to a reception in Madame Victor Hugo's salon in Paris reported that "the excitement was something tremendous, and for a time you could hear the sound of ss ss ss running through the room as there passed from mouth to mouth the exclamation 'C'est Simpson, C'est Simpson' " (Simpson, A. R., 1911).

Simpson died of coronary disease on 6th May, 1870, at age 58, and was buried in Warriston Cemetery in Edinburgh, alongside the five of his nine children who had predeceased him. A day of public mourning was declared in Edinburgh, its shops and the University were closed, and it is said that thirty thousand bereaved citizens attended the funeral. A bust of Simpson, erected in Westminster, bears the inscription, "To whose Genius and Benevolence the world owes the blessings derived from the use of Chloroform for the relief of suffering," a fitting but modest tribute to one of nature's true noblemen.

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TRIPLET PREGNANCY WITH PERSISTENT TRANSVERSE LIE OF THE PRESENTING FOETUS

BY

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THE occurrence of persistent transverse lie of the presenting foetus is rare in multiple pregnancy. In 600 cases of twins recently reported the incidence was 0·3 per cent (Fink, 1955). In triplet pregnancy the condition must be extremely rare. In the series of triplets reported by Beacham and Beacham (1950), Fink (1955), and Tran-Dink-De and Vo-Liet-Nu (1956), the lie of the first foetus was longitudinal in every case. This case is considered rare enough to be reported.

CASE REPORT

Mrs. M.P. was aged 28 years when first seen in November, 1954. She had had 2 previous pregnancies and 2 miscarriages. The largest infant was 7 pounds and 7 ounces at birth. The previous medical history was good. There was a history of multiple pregnancy on both sides of the family. Mrs. P. belonged to blood group O, was Wassermann negative and Rhesus negative. There were no rhesus antibodies in her serum, nor did any develop in this pregnancy. The last menstrual period commenced 25th August, 1954 and the expected date was 1st June, 1955. Medical examination was carried out at booking clinic and no abnormality was noted. The patient's weight was 10 stones 5 pounds and her height was 5 feet 2 inches. Vaginal examination showed that the uterus was enlarged to the size of a 10-weeks pregnancy, and that the pelvis was of ample dimensions. She was seen at the clinic regularly. At 24-weeks gestation the uterus was larger than normal and a radiograph showed triplets. Following this Mrs. P. was seen weekly. She was admitted to hospital at 26-weeks gestation as a prophylactic measure against premature labour.

On admission her blood pressure was 125/65 mm. Hg and the urine was clear. The patient's weight was now 12 stones 2 pounds. She was kept in bed and allowed up only for toilet purposes. Progress in hospital was uneventful. At 30-weeks gestation the girth of the abdomen was 46 inches and the patient's weight was 12 stones 8 pounds. The blood pressure and urine were normal. Multiple foetal heart sounds were present. At 34 weeks the girth was 48 inches and the patient's weight was 13 stones 3½ pounds. There was mild clinical oedema. The presenting part of the lowermost foetus was not known, and a radiograph of the abdomen (see photograph) showed the first foetus lying transversely with the head in the right iliac fossa. The two other triplets were presenting as a breech and a vertex. Some degree of maternal oedema persisted, in spite of bed rest and salt restriction. At 38 weeks the blood pressure had risen to 140/90 mm. Hg and a trace of albumin appeared in the urine. Her weight was 13 stones and 6 pounds. It was decided to induce labour. At this time no presenting part could be felt in the pelvis and a further X-ray, directed to the lowermost foetus, showed that it was still lying transversely. Vaginal examination was made under aseptic conditions. The cervix was 2-fingers dilated, soft and loosely applied. No foetal part occupied the pelvis. Under nitrous oxide and oxygen anaesthesia the cervix was stretched, and the membranes were swept. Labour did not follow. On the next day, an intravenous drip of 5 per cent glucose containing Pitocin 2 units per half litre was commenced at 10 drops per minute. Regular weak uterine contractions followed. After 2 hours the contractions occurred once in 5 minutes and lasted 20 seconds. After labour had been in progress 4 hours and 30 minutes a vaginal examination was made to assess progress. The cervix was 3-fingers dilated and soft and a tense bag of membranes was felt. Under general anaesthesia the cervix was stretched to 4-fingers dilatation, and a hand was passed into the uterus. The membranes were ruptured, and the foot of the presenting foetus was secured and drawn into the vagina. A one pound weight was attached to the foot by means of a fillet. Uterine contractions followed and after 30 minutes the posterior buttock of the first baby was on the perineum. Pudendal block anaesthesia was now carried out, using 1 per cent lignocaine hydrochloride. Assisted breech delivery of a living infant followed. Episiotomy was done and forceps were applied to the aftercoming head. Vaginal examination now showed that the second triplet presented as a breech with flexed legs. The membranes of the second sac were punctured, and the second triplet was born spontaneously as far as the head. The aftercoming head was delivered with forceps. Further vaginal examination revealed a shoulder presentation of the third triplet. Under general anaesthetic internal podalic version and breech extraction were done. The second stage of labour occupied 50 minutes. The third stage was completed spontaneously after 15 minutes. There was no postpartum haemorrhage. The pitocin drip was continued

FIG. 1
Radiogram showing transverse lie of presenting triplet.

until labour was completed. It was discontinued only when the internal versions were being done.

The first two triplets were females and weighed 5 pounds 8½ ounces and 5 pounds 10½ ounces. The third was a male and weighed 5 pounds 14½ ounces. The placenta was trinovular. The total duration of labour was 5 hours 55 minutes. The puerperium was uneventful.

Mother and babies were discharged after 14 days.

Comment

The chief interest in this case lay in the persistence of a transverse lie in the presenting triplet. The appearance of toxaemia indicated termination of the pregnancy at 38-weeks gestation. Caesarean section was considered as a method of treatment. The maternal hazards of this operation must be increased when carried out as an elective procedure in a triplet pregnancy. Good contraction and retraction of the overdistended uterus might be difficult to obtain, with considerable risk of haemorrhage from the large placental site. The alternative management was to induce labour and to correct the malpresentation by internal methods when labour was established. This was the method chosen. It offered the chance of a vaginal delivery to the mother and, although there was the known risk of internal version to the first triplet, spontaneous delivery of the second and third triplets was expected from their positions on the radiograph. Furthermore, the risk to the foetus of internal version is probably less in multiple pregnancy, due to the greater facility with which it can be done. The method of induction to be chosen excluded membrane puncture. In this case it consisted of sweeping the membranes followed by a Pitocin drip. Normally Pitocin is contra-indicated in the presence of a malpresentation. In this case it was used initially to induce labour and later to maintain it. I felt that its use contributed to the successful outcome of the case and in particular to the safe delivery of the first triplet. Continuation of the drip until completion of the third stage of labour was a safeguard against postpartum haemorrhage. Finally, admission of the patient to hospital at 26-weeks gestation was considered an important measure in maintaining the pregnancy to 38 weeks, and obtaining babies of good size.

I thank Miss I. R. Bishop for permission to publish the case and Miss Mason for the photograph.

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STANDARD FORM RECOMMENDED BY THE ROYAL COLLEGE OF OBSTETRICIANS AND GYNAECOLOGISTS FOR THE PRODUCTION OF MATERNITY HOSPITAL MEDICAL REPORTS

In 1948 the Council of the College stated "The College is firmly of the opinion that the publication of a medical report is of extreme value in maintaining a high standard of practice, and would go so far as to urge all maternity hospitals and departments to publish an annual report. The standard form now recommended closely follows the form used in the past and if it can be widely adopted the value of the information obtained will be enhanced by the possibility of comparisons over a number of years."

The standard form of annual Maternity Hospital Report referred to above was published in the Journal in 1948 (*J. Obstet. Gynaec. Brit. Emp.*, **55**, 479–495).

The recommended Report has been widely adopted in Great Britain and the Commonwealth. Because of the steadily increasing cost of publication however, the Council asked its Special Committee to consider if a shortened form of Report could be recommended. The Committee reported that to shorten the Report sufficiently to reduce the cost of production effectively, would destroy the value of the Report. Accordingly Council recommends that the Standard form should be produced in every maternity hospital and department and retained, but that a summary only need be printed for general distribution.

The Committee has reviewed the Standard form in the light of comments received from time to time. These recommendations have been accepted by Council. In the place of the former "toxaemia" table it now suggests four tables entitled Pre-eclampsia, Essential Hypertension, Chronic Nephritis, and Unclassified "Toxaemia" respectively. Similarly it suggests that ante-partum haemorrhage should be recorded in three tables, Placenta Praevia, Accidental Haemorrhage, and Ante-partum Haemorrhage of Doubtful Origin. The Contracted Pelvis table is replaced by one for Disproportion. Certain minor modifications will be found in the Obstetric Section. In the Paediatric Section some minor changes have been made and a new table for Haemolytic Disease has been included.

Certain suggestions were made which the Committee was unable to adopt. It was thought impracticable, for example, to attempt to define pre-eclamptic toxaemia; a table for post-maturity or for diabetes and pregnancy was not recommended. It is recognized that individual hospitals may find it desirable to make additions to, or modifications of, the scheme as now recommended.

For convenience the full Report is reproduced here and embodies the changes, thus replacing the 1948 recommendation.

As before, Messrs. Wilding and Sons, Ltd., Castle Street, Shrewsbury, will set up and retain the recommended headings from which they can print the necessary report books from which compilation is made.

October, 1957.

I. THE OBSTETRICS SECTION

TABLE 1. **ABORTION**

(Expulsion of products of conception before completion of the 28th week of pregnancy.)

Booked or non-booked	Reg. No.	Age	Previous Pregnancies		Maturity	If induced: indication and method	If spontaneous: cause (if known) and treatment	Result	Morbidity	Remarks
			Before 28 weeks	After 28 weeks						

TABLE 2. **HYPEREMESIS ADMITTED FOR TREATMENT**

Booked or non-booked	Reg. No.	Age	Previous Pregnancies		Maturity on admission	Treatment	Result		Remarks
			Before 28 weeks	After 28 weeks			M.	C.	

TABLE 3. **CARDIAC DISEASE**

Booked or non-booked	Reg. No.	Age	Previous Pregnancies		Lesion	Degree of failure of compensation. (Class 1, 2, 3 or 4. N.Y. Heart Assoc., 1939)		Maturity at delivery	Method of delivery	Result		Remarks
			Before 28 weeks	After 28 weeks		On admission	At delivery			M.	C.	

TABLE 4. PRE-ECLAMPSIA

Booked or non-booked	Reg. No.	Age	Previous Pregnancies		Maturity		Albuminuria		Oedema	Highest blood pressure	No. of days in hospital before labour or discharge	If labour induced state method	Method of delivery	Result		Weight of child	Remarks
			Before 28 weeks	After 28 weeks	On admission	At delivery	Maximum	On discharge						M.	C.		

TABLE 5. ESSENTIAL HYPERTENSION

Booked or non-booked	Reg. No.	Age	Previous Pregnancies		Maturity		Albuminuria		Oedema	Highest blood pressure	No. of days in hospital before labour or discharge	If labour induced state method	Method of delivery	Result		Weight of child	Remarks
			Before 28 weeks	After 28 weeks	On admission	At delivery	Maximum	On discharge						M.	C.		

TABLE 6. CHRONIC NEPHRITIS

Booked or non-booked	Reg. No.	Age	Previous Pregnancies		Maturity		Albuminuria		Oedema	Highest blood pressure	No. of days in hospital before labour or discharge	If labour induced state method	Method of delivery	Result		Weight of child	Remarks
			Before 28 weeks	After 28 weeks	On admission	At delivery	Maximum	On discharge						M.	C.		

TABLE 7. UNCLASSIFIED "TOXAEMIA"

Booked or non-booked	Reg. No.	Age	Previous Pregnancies		Maturity		Albuminuria		Oedema	Highest blood pressure	No. of days in hospital before labour or discharge	If labour induced state method	Method of delivery	Result		Weight of child	Remarks
			Before 28 weeks	After 28 weeks	On admission	At delivery	Maximum	On discharge						M.	C.		

TABLE 8. ECLAMPSIA

(A general statement of the treatment used should accompany this table.)

TABLE 8. **ECLAMPSIA**

(A general statement of the treatment used should accompany this table.)

Booked or non-booked	Reg. No.	Age	Previous Pregnancies		Maturity at delivery	Condition on admission	If in labour	FITS					URINE			Oedema	Highest blood pressure	No. of days in hospital before delivery	If induced state method	Method of delivery	Result		Remarks
													Albumin										
			Before 28 weeks	After 28 weeks				Before admission	Ante-partum	Intra-partum	Post-partum	Total	On admission or maximum	On discharge	Quantity in first 24 hrs.						M.	C.	

TABLE 9. **PLACENTA PRAEVIA**

Booked or non-booked	Reg. No.	Age	Previous Pregnancies		Maturity			Condition on admission	If in labour	Type 1, 2, 3, 4	Treatment	Blood transfusion	Amount of bleeding	Result		Remarks
			Before 28 weeks	After 28 weeks	At 1st haem'h'ge	On admission	At delivery							M.	C.	

TABLE 10. **ACCIDENTAL HAEMORRHAGE**

Booked or non-booked	Reg. No.	Age	Previous Pregnancies		Maturity			Condition on admission	If in labour	Treatment	Blood transfusion	Amount of Bleeding		Result		Remarks
			Before 28 weeks	After 28 weeks	At 1st haem'h'ge	On admission	At delivery					Concealed	Revealed	M.	C.	

TABLE 11. **ANTEPARTUM HAEMORRHAGE OF DOUBTFUL ORIGIN**

Booked or non-booked	Reg. No.	Age	Previous Pregnancies		Maturity			Condition on admission	If in labour	Treatment	Blood transfusion	Amount of bleeding	Result		Remarks
			Before 28 weeks	After 28 weeks	At 1st haem'h'ge	On admission	At delivery						M.	C.	

TABLE 12. GROSS HYDRAMNIOS

Booked or non-booked	Reg. No.	Age	Previous Pregnancies		Maturity		Treatment	Result		Foetal abnormalities	Remarks
			Before 28 weeks	After 28 weeks	On diagnosis	At delivery		M.	C.		

TABLE 13. TUMOURS ASSOCIATED WITH PREGNANCY, LABOUR OR PUERPERIUM

Booked or non-booked	Reg. No.	Age	Previous Pregnancies		Nature of tumour	Treatment	Result		Remarks
			Before 28 weeks	After 28 weeks			M.	C.	

TABLE 14. PROLONGED LABOUR
(Arbitrary definition being labour lasting 36 hours or more.)

Booked or non-booked	Reg. No.	Age	Maturity	Previous Pregnancies		Presentation and Position of Foetus		Cause of delay as diagnosed	Time of rupture of membranes, i.e., hours before delivery	Duration of Labour			Treatment	P.P.H.	Morbidity	Method of delivery	Weight of child	Result		Child	
				Before 28 weeks	After 28 weeks	At onset of labour	At delivery			1st stage	2nd stage	3rd stage						M.	C.	Trauma	Resuscitation Yes/No

TABLE 15. PERSISTENT POSTERIOR POSITION OF THE OCCIPUT AND TRANSVERSE ARREST

Booked or non-booked	Reg. No.	Age	Previous Pregnancies		Maturity	Position of occiput	Type of pelvis if known	Treatment	Result		Weight of child	Remarks
			Before 28 weeks	After 28 weeks					M.	C.		

TABLE 16. UNCOMPLICATED BREECH DELIVERIES
(i.e., without other obstetric abnormality. Includes cases with extended limbs.)

TABLE 16. **UNCOMPLICATED BREECH DELIVERIES**
(i.e., without other obstetric abnormality. Includes cases with extended limbs.)

Booked or non-booked	Reg. No.	Age	Previous Pregnancies		Maturity	Legs flexed or extended	Method of delivery	Result		Weight of child	Episiotomy or tear	Remarks
			Before 28 weeks	After 28 weeks				M.	C.			

TABLE 17. **COMPLICATED BREECH DELIVERIES**
(Excluding breech by version in labour.) This table includes breech delivery where some other obstetric complication is present, e.g., contracted pelvis, placenta praevia, twins, toxaemia, prolapsed cord.

Booked or non-booked	Reg. No.	Age	Previous Pregnancies		Maturity	Obstetric complication	Treatment	Result		Weight of child	Episiotomy or tear	Remarks
			Before 28 weeks	After 28 weeks				M.	C.			

TABLE 18. **FACE AND BROW PRESENTATIONS**

Booked or non-booked	Reg. No.	Age	Previous Pregnancies		Maturity	Position	Treatment	Method of delivery	Result		Weight of child	Remarks (e.g., anencephaly)
			Before 28 weeks	After 28 weeks					M.	C.		

TABLE 19. **TRANSVERSE AND OBLIQUE LIE**
(In labour.)

Booked or non-booked	Reg. No.	Age	Previous Pregnancies		Maturity	Obstetric compli-cation	Size of os when diagnosed	Treatment	Result		Weight of child	Remarks
			Before 28 weeks	After 28 weeks					M.	C.		

TABLE 20. MULTIPLE PREGNANCY

Booked or non-booked	Reg. No.	Age	Previous Pregnancies		Maturity	Presentation		Method of delivery		Sex		Weight		Type if known	Result			Remarks
			Before 28 weeks	After 28 weeks		1st	2nd	1st	2nd	1st	2nd	1st	2nd		M.	1st	2nd	

TABLE 21. LABOUR FOLLOWING PREVIOUS CAESAREAN SECTION

Booked or non-booked	Reg. No.	Age	Previous Pregnancies		Maturity	Previous Caesarean Section			Method of delivery	Weight of baby	Result		Remarks
			Before 28 weeks	After 28 weeks		Indication	Weight of baby	Type of C.S.			M.	C.	
						1. 2. 3.							

TABLE 22. DISPROPORTION

Booked or non-booked	Reg. No.	Age	Previous Pregnancies		Maturity	Cause of disproportion including any pelvic abnormalities	Management	Length of Labour		Weight of child	Result		Morbidity	Remarks
			Before 28 weeks	After 28 weeks				1st stage	2nd stage		M.	C.		

TABLE 23. FAILED FORCEPS

Booked or non-booked	Reg. No.	Age	Previous Pregnancies		Maturity	Failed Forceps		Cause of failure	Treatment and method of delivery	Weight of child	Result		Remarks
			Before 28 weeks	After 28 weeks		Before admission	After admission				M.	C.	

TABLE 24. PROLAPSE AND PRESENTATION OF CORD

TABLE 24. PROLAPSE AND PRESENTATION OF CORD

Booked or non-booked	Reg. No.	Age	Previous Pregnancies		Maturity	Size of os when diagnosed	Cause of prolapse or presentation of cord	Treatment	Result		Remarks
			Before 28 weeks	After 28 weeks					M.	C.	

TABLE 25. POST-PARTUM HAEMORRHAGE

(Primary P.P.H. by convention over 20 oz. and within 24 hours of delivery. Secondary P.P.H. includes any appreciable haemorrhage occurring subsequently during the puerperium.)

Booked or non-booked	Reg. No.	Age	Previous Pregnancies		Maturity	Method of delivery	Duration of labour	Amount of Haemorrhage			Cause or predisposing factor	Treatment. State drug, dose and route	Blood transfusion	Remarks
			Before 28 weeks	After 28 weeks				Before delivery of placenta	After delivery of placenta	Secondary P.P.H.				

TABLE 26. MANUAL REMOVAL OF PLACENTA

Booked or non-booked	Reg. No.	Age	Previous Pregnancies		Maturity	Method of delivery	Length of Labour			Indication	Amount of bleeding oz.	Morbidity	Result to mother	Remarks
			Before 28 weeks	After 28 weeks			1st stage	2nd stage	3rd stage					

TABLE 27. EXTERNAL VERSION AFTER 32 WEEKS

(This table may be summarized if desired.)

Booked or non-booked	Reg. No.	Age	Previous Pregnancies		Maturity		Indication flexed breech, extended breech, transverse lie	Position of legs confirmed by X-ray. Yes. No.	Anaesthetic, if employed	Presentation at delivery	Result		Remarks
			Before 28 weeks	After 28 weeks	At version	At delivery					M.	C.	

TABLE 28. SURGICAL INDUCTION OF LABOUR

Booked or non-booked	Reg. No.	Age	Previous Pregnancies		Maturity	Indication	Method of induction	Induction delivery interval	Method of delivery	Duration of Labour		Weight of child	Result		Remarks
			Before 28 weeks	After 28 weeks						1st stage	2nd stage		M.	C.	

TABLE 29. CAESAREAN SECTION

Booked or non-booked	Reg. No.	Age	Previous Pregnancies		Maturity	Previous C.S.	Indication	Anaesthetic used	Type of operation	If sterilized	Duration of Labour		Weight of child	Result		Morbidity	Remarks
			Before 28 weeks	After 28 weeks							1st stage	2nd stage		M.	C.		

TABLE 30. FORCEPS DELIVERY

Booked or non-booked	Reg. No.	Age	Previous Pregnancies		Maturity	Indication	Anaesthetic	Duration of Labour		Weight of child	Result		Child		Remarks
			Before 28 weeks	After 28 weeks				1st stage	2nd stage		M.	C.	Trauma	Resuscitation Yes or No	

TABLE 31. EMBRYOTOMY AND CRANIOTOMY

Booked or non-booked	Reg. No.	Age	Previous Pregnancies		Maturity	Indication	Duration of Labour		Type of operation	Weight of child	Result to mother	Remarks
			Before 28 weeks	After 28 weeks			1st stage	2nd stage				

TABLE 32. PUERPERAL PYREXIA, GENITAL INFECTION

TABLE 32. PUERPERAL PYREXIA, GENITAL INFECTION

Booked or non-booked	Reg. No.	Age	Maturity	Method of delivery. Operation, induction, manual removal, etc.	Organisms, if known	Treatment	Result	Remarks

TABLE 33. PUERPERAL PYREXIA, EXTRA-GENITAL INFECTION

Booked or non-booked	Reg. No.	Age	Maturity	Method of delivery. Operation, induction, manual removal, etc.	Site	Organisms, if known	Treatment	Result	Remarks

TABLE 34. ASSOCIATED DISEASES AND CONDITIONS NOT DETAILED ELSEWHERE

Booked or non-booked	Reg. No.	Age	Previous Pregnancies		Disease or Condition	Treatment	Result		Remarks
			Before 28 weeks	After 28 weeks			M.	C.	

MATERNAL DEATHS

1. .....
2. .....
3. .....

SPECIAL CASES

Details of special and particularly interesting cases should be given separately.

1. .....
2. .....
3. .....

II. PAEDIATRIC SECTION

TABLE 35. STILLBIRTHS

For the purposes of this report a stillborn child is defined as one born at or after the completion of the 28th week of pregnancy and which fails to breathe after birth.

Booked or non-booked	Reg. No.	Weight	Maturity of foetus	Sex	Method of delivery	Maternal factors	Foetal factors	P.M. findings (if no P.M. state "not done")	Remarks including cause of death

TABLE 36. NEONATAL DEATHS

Deaths within 28 days either in the hospital or after transfer to another hospital but excluding those discharged healthy.

Booked or non-booked	Reg. No.	Birth Weight	Maturity of foetus	Sex	Method of delivery	Maternal factors	Complications in infant	P.M. findings (if no P.M. state "not done")	Age at death	Remarks including cause of death

TABLE 37. PREMATURE LIVE-BORN INFANTS

(Birth weight 5½ pounds and under.)

Booked or non-booked	Reg. No.	Maturity	Birth Weight	Sex	Cause of premature labour	Birth trauma, if any	Weight on discharge	Day of discharge or death	Result	Remarks

TABLE 38. CONGENITAL MALFORMATIONS

TABLE 38. CONGENITAL MALFORMATIONS

Booked or non-booked	Reg. No.	Nature of malformation	Birth weight	Sex	Result	Remarks

TABLE 39. BIRTH TRAUMA

Booked or non-booked	Reg. No.	Maturity	Birth weight	Sex	Nature of trauma	Method of delivery	Result	Remarks

TABLE 40. NEONATAL INFECTIONS

Booked or non-booked	Reg. No.	Maturity	Birth weight	Sex	Nature of infection	Predominant causal organism	Treatment	Result	Remarks

TABLE 41. HAEMOLYTIC DISEASES

Booked or non-booked	Reg. No.	History of previous pregnancies	Mother's blood group and Rh. state	Father's genotype (if known)	Antibodies when first detected	Abnormalities of pregnancy or labour	Maturity at birth	Sex	Birth weight	Condition at birth	Child's blood group and Rh. state	Treatment. Age in hours when begun	Progress

TABLE 42. OTHER NEONATAL DISEASES

Booked or non-booked	Reg. No.	Maturity	Birth weight	Sex	Type of disease	Maternal complication	Method of delivery	Treatment	Result	Remarks

Obituary

CHARLES DAVID READ

Kt., M.B., Ch.B.(N.Z.), P.R.C.O.G., F.R.C.S., F.R.C.S.E., F.R.A.C.S.

MEDICINE and not Obstetrics and Gynaecology alone has suffered a great loss with the sudden and untimely death of Sir Charles Read. Outstanding in so many ways, he was a natural and undisputed leader and an adornment to the profession. Had the years been spared to him he would have taken his place modestly, but assuredly, as an elder statesman of a calibre always needed, but all too seldom found.

Charles Read was born in Dunedin, New Zealand, on 22nd December, 1902, and spent his boyhood in a small country town in the South Island. After graduating from Otago in 1924 (Medallist in Clinical Medicine), he spent two years resident at Dunedin in the teaching hospital of his medical school. He then travelled 12,000 miles in search of further experience in London, where began his association with the Chelsea Hospital for Women which was to flourish to the honour and prestige of both until the time of his death. The story of his phenomenal success is an inspiring record. In a relatively few years he had by sheer merit been acclaimed in Great Britain and internationally as an outstanding exponent of Gynaecology and Obstetrics. The many honours which were showered upon him, forerunners of the even greater ones which must inevitably have been bestowed, were accepted so graciously and modestly that the manner of their acceptance added still further to his stature.

Charles Read began his training in Britain as house surgeon at the Chelsea Hospital for Women, where he immediately attracted the attention of Mr. Victor Bonney and Mr. Bright Bannister, among others. Both of these men, who were then at the height of their fame, recognized his great talents and encouraged him in many practical ways to stay and practise in London. Those were the days when Bonney was recognized as the great master and Charles proved himself a most apt pupil of his internationally famous chief. He quickly realized the importance of technique in making surgery safe, and his quick, decisive mind enabled him to learn rapidly from all who could teach him and to develop methods best suited to his own temperament. He was always a perfectionist and operations which brought him spontaneous applause from the gallery would often leave him dissatisfied and determined to make the technique better still. One result was that even as a junior surgeon at Chelsea he was becoming known as one of London's finest operators. Those who knew his work more intimately were well aware that surgery meant much more to Charles than many of those who watched and admired his operating realized. The operation was but one episode, though an important one, in his relationship with his patient. As pathologist to Chelsea Hospital for Women, a position he held for five years during his early days, he became experienced and highly skilled until his opinion on a difficult specimen or section was one well worth obtaining. A junior surgeon at Chelsea at that time assisted his senior at all operations, had few beds at his disposal, and was responsible for one outpatient session a week. It was typical of Charles Read that a rapidly growing private practice was not allowed to interfere with his hospital commitments. It was equally typical that years later when he became a senior surgeon he made it possible for every surgeon to have equal access to the available beds. Throughout his life he scrupulously and most generously fulfilled his obligations. As a junior surgeon he was always in the theatre when due to assist, and

By courtesy of Fayer

CHARLES DAVID READ

was most punctual and regular in attending at out-patients. His sensitive fingers were uncanny in detecting the details of physical signs, and this together with his knowledge of pathology made his accuracy of diagnosis as impressive as his operative skill, or his judgment on when to operate and what to do. After a long association with Charles and his work it is an inspiration and a joy to record that his assessment of a clinical problem was so consistently accurate that one learned to regard the diagnosis signed by those familiar initials "C.D.R." as being almost infallible.

Charles was the hero of the many who followed him in the path of apprenticeship he had trodden at Chelsea. He was the complete surgeon, but also he was the perfect example of the extremely busy man who was never in a hurry. The confidence of patients was quickly gained for there were few who failed to respond to his direct, kindly, and sympathetic approach. His generosity to younger colleagues was remarkable and as a result heavy demands were made on his time and energy by medical men and their families. He was particularly generous to younger men from the Commonwealth, many of whom will always be grateful for his wise counsel and support, as well as for the medical skill he gave so freely.

During his early years in London Charles was on the junior teaching staff of both Charing Cross and Westminster Hospitals. He was a magnificent teacher, lucid, practical, humorous and authoritative, and would have been an asset to any hospital. He was too fine a man to reveal his disappointments and even his close friends could not know just how much he regretted not being appointed to the consulting staff of a London teaching hospital, but those who knew his worth realized that the loss was theirs as much or more than his. It was a great joy to him and to his friends and admirers when in 1950 he was appointed Director of the Institute of Obstetrics and Gynaecology of the British Post-Graduate Medical Federation in the University of London. This important post gave him the recognition he so richly deserved and even greater opportunities than he had previously possessed as Director of Post-Graduate Studies at the Chelsea Hospital for Women. It was characteristic of Charles that having accepted this great honour he immediately replanned his life so that he could contribute the most to this new work. He gave up his Harley Street practice and strictly limited his private activities to his clinic in Queen's Gate, which was close to his headquarters at Chelsea Hospital for Women. His appointment was an unqualified success and with a wider sphere of influence his outstanding qualities of both performance and leadership became progressively more apparent. His capacity for friendship seemed unlimited as was his memory for people, the places from which they came, and the important details of their lives and work. The stranger immediately felt at ease in his presence and soon felt at home, marvelling at the knowledge Charles revealed of mutual friends and acquaintances, even in distant parts of the earth.

Charles Read had been discovered by our American colleagues many years previously and they held him in the highest regard. It would be safe to say that no medical man has done more for Anglo-American friendship. In 1949 he delivered the Joseph Price Oration at Hot Springs, Virginia, to the American Association of Obstetricians, Gynaecologists and Abdominal Surgeons, of which he was made an Honorary Fellow. He subsequently accepted many invitations to visit the North American continent to give important lectures and to take part in conferences and congresses. He was constantly anxious to foster good relations with America and to encourage the active interchange of men and ideas with our American colleagues. He looked forward to the day when there would be reciprocity for teaching purposes and examination requirements between selected post-graduate schools in Great Britain and America, and he more than any other helped to initiate the enquiries now in progress concerned with making this possible.

The honours he received in America he modestly interpreted as tokens of approval of the ideals for which he worked rather than as personal tributes. He was particularly delighted at being elected an Honorary Fellow of the American Gynecological Society. He was also an Honorary Fellow of the Athens Obstetrical

and Gynaecological Society, a Fellow of the Hunterian Society and the Harveian Society, a Fellow of the Royal Society of Medicine, in which he had been a Vice-President of the Obstetric Section. He had been an examiner for the Royal College, for the Universities of Birmingham and Glasgow, and for the Central Midwives Board. Among other important lectures he had delivered in Great Britain were the Ingleby lectures at Birmingham University, and the Litchfield lecture at Oxford. His reputation as a lecturer was international and richly deserved. Attention to detail was the basis of his success and he realized that in public speaking, as in surgery, technique was most important. Illustrations were perfectly prepared and he was an authority on how slides should be used to make the greatest contribution to the presentation of a subject. There was no straining of the eyes to catch the details of illegible or overfilled slides when Charles was lecturing. He fully appreciated the advantages and the disadvantages of white on black and how to make the greatest use of colour. None knew better than he that "ars est celare artem" and his lectures and orations, like his operating, were so brilliantly effortless that many not knowing him would fail to realize how much thought and practice he had devoted to achieving the final polished result.

Charles had seriously considered writing a new gynaecological textbook with one or two of his friends and would probably have done so had he lived longer. The revised fifth edition of Eden and Lockyer, for which he was responsible with his colleague Mr. Douglas MacLeod, was a great success and he was engaged with the same author on revising the textbook of gynaecological surgery written by their former chief, Victor Bonney. His wide experience and lucid powers of expression made him an ideal contributor to medical literature.

Charles commenced his active association with the Royal College of Obstetricians in 1940, when he was appointed to the Examination Committee, of which he was elected Chairman in 1949. He was co-opted to Council the same year as Chairman of the Examination Committee and served on it until 1952, but was again co-opted in 1954, and was elected President in 1955. Prior to this he had served with distinction on many important College committees, including the Hospital Recognition, Fellowship Selection, Dominions, and Journal Committee. His clear thinking and ability to recognize essential facts, even when concealed in a maze of detail, made him a most valuable committee man, and his contributions to the College were many and varied. In recent years he was particularly interested in the new building project and he more than any other member of Council was responsible for the plans of the new College. His joy was great when Lord Nuffield by his magnificent gift made it possible for the final steps to be taken to transfer plans into the new buildings in Regents Park. The Knighthood conferred upon him in the Birthday Honours this year was a worthy tribute to the great work he had already done for the College as well as to his eminence in international medicine.

In this chronicle of some of the qualities and achievements of a very great man it is fitting to record brief mention of his courage. On a number of occasions during his life he faced great personal danger, as when he was gravely injured in an accident involving an American army lorry and his car. He was always uncomplaining and unafraid. When in his late forties, while at the height of his power, he received the grim but fortunately transient warning while operating that his heart was much larger than the calibre of his arteries, he accepted the warning with characteristic fortitude. A short rest, a voyage to South Africa on the sea he loved so dearly, a replanning of his professional life to free him from the heavy demands of his obstetric practice, and he was back in full harness. Where lesser men would have curtailed their activities and lived anxiously he lived abundantly and accepted newer and greater responsibilities, including the post of Director of the Post-Graduate Federation and the high office of President of the Royal College. He fully realized the possible implications of these decisions. When in 1955 he was urged by many of his colleagues in Council to accept nomination for the Presidential election he confessed to a friend that if there was any contribution he could make to the College he must do it "now or never". It was characteristic of Charles that

having made his decision there was no looking back. All his energy and great ability were marshalled for the arduous duties he had accepted and he gave of himself happily and unsparingly. His visit to South Africa in 1956 to inaugurate the South African Regional Council was a personal triumph and did much for the prestige of the College in the Union. In both British and Afrikaans centres subsequent visitors heard repeated and glowing tributes to Charles and the success of his tour, but this was the same sequence wherever he went.

As already stated, he loved the sea and was never happier than when on a fine ship. After his illness five years ago he spent more time in relaxing at weekends on his motor yacht, "Taurima" and later on its magnificent successor, "Taurima II". Many of the great number of those privileged to share happy hours with Sir Charles and Lady Read on these vessels would not have known that "Taurima" is a Maori word meaning "hospitality". No more appropriate name could have been chosen, for Charles and Edna were a perfect host and hostess and "Taurima II", which was a great joy to Charles, was a magnificent ship and beautifully equipped. When the President left his last meeting of the College Council he confessed he was a very tired man. His much needed holiday was due to begin and his many friends were glad to learn that he was able to share with his family the cruising he so much enjoyed in France and the Channel Islands. "Taurima II" had returned to Dartmouth when the tragedy occurred and the family he dearly loved, with whom he had shared his holiday, were so suddenly bereaved. For Charles it was a fitting end and perhaps for those he loved there is comfort to be found in the manner of his passing. He had lived his life to the full and achieved more than is possible to most men. Had illness crippled him, as it could so easily have done, he would have accepted the blow with his usual smile and great fortitude, but death came swiftly and with mercy.

In his lifetime Charles Read was a legendary figure to many throughout the world. Now that he has gone his name will be recorded among the great in the chronicles of British medicine and we who were privileged to know him are the richer for the inspiration of his friendship.

JOHN STALLWORTHY.

THE death of the President of our College has struck a harsh blow to Obstetrics and Gynaecology throughout the world. The loss of Sir Charles Read will be felt over many years.

This man truly was big. He carried a huge frame but a much larger "heart". His warmth and friendliness to everyone could be felt. He was one of the few men in big, cold London Town to whom anyone from the far-flung corners of the Commonwealth or world could turn.

He had a brilliant memory, remembering the names and abodes of all his friends. As a matter of fact I have yet to meet the person who had come into contact with Charles Read who was not a friend of his.

We in South Africa greatly admired and loved him. How pleased we were when, after his illness in 1952, he came out here on a recuperative visit. Knowing him better and appreciating the depth of the man, we were so happy to find that the College had elected him President. We were proud and shared the honour of the knighthood Her Majesty bestowed upon him.

We were fortunate to have him—as College President—inaugurate the South African Regional Council in 1956. During that time he also attended the Obstetrical and Gynaecological Congress, taking an active part in all discussions and presenting a paper himself. He mixed with and became a friend of everyone attending that particular Congress.

He was a brilliant teacher, who obviously worked up his subject thoroughly before a lecture. He had an excellent knowledge of pathology and had the great ability of being able to impart it simply and practically.

As an operator he can justly be described as having been delicately artistic, ranking amongst the very best in the world. It was in the theatre of the Chelsea Hospital for Women that the Commonwealth's present and future gynaecologists, indeed men from all over the world, met, in order to study his display of artistry and to enjoy the permeating warmth of his personality.

By being such an excellent "drawing-card" to Chelsea, he did more than teach his spectators gynaecology. It was with a spirit of anticipation that one went there, wondering not whether, but how many, old friends from all over the world would be met in the gallery, or having coffee with him in Sister's room.

As President of the College he drew us all nearer to each other by infusing his easy manner and warmth into the newsletters.

We mourn this heavy loss and extend our warmest sympathy to his widow and four sons, and to the Royal College of Obstetricians and Gynaecologists. JAMES T. LOUW.

JOHN PRESCOTT HEDLEY

JOHN PRESCOTT HEDLEY

(1876–1957)

JOHN PRESCOTT HEDLEY, Jock to all who knew him, died on Wednesday, 17th July, in St. Thomas's after the briefest illness. Although he would be the last to acknowledge it he was a most distinguished man.

Born in 1876, he was the son of John Hedley, M.D., J.P., of Middlesbrough. From Uppingham he went to King's College, Cambridge, and thence to St. Thomas's. His connexion with the Hospital was unbroken for nearly 60 years, for following his retirement from the active staff in 1936 he became a member of the Council of the Medical School and attended, apparently in good health, the last meeting of that body only two weeks prior to his death.

His academic distinctions are best listed as follows: In 1902 he acquired the degrees M.A.(Camb.) and M.B., B.Ch. A Member of the Royal College of Physicians in 1907 he was elected a Fellow fourteen years later. In 1909 he was made a Fellow of the Royal College of Surgeons of England and also was awarded the degree of M.Ch.

After holding several resident posts at St. Thomas's he started on his specialist career as Obstetric Tutor and Registrar (1907–1910). Finally he was appointed Obstetric Physician to the Hospital in 1911. His only other appointment was to the Staff of the General Lying-In Hospital, York Road. He examined at Cambridge, at Edinburgh, and for the Conjoint and Central Midwives Board.

He joined the Worshipful Society of Apothecaries, London, in 1915 and was made a member of the Court of the Society in 1938. He was Master 1944–45. He had a great affection for this Society and its activities and was appointed as the Society's representative on the Central Midwives Board in 1938. For six years he acted as Vice-Chairman of the C.M.B. until his resignation in 1952. In 1939 he was elected as representative of the Society of Apothecaries to the General Medical Council on which he served up to the time of his death. A foundation Fellow of the Royal College of Obstetricians and Gynaecologists, he served on the Council from 1937 to 1945 and for six years as Honorary Treasurer. This then was his academic background.

Although it is now 21 years ago since Jock Hedley retired from the staff of St. Thomas's he had continued until his death a most active association with his old hospital. He undoubtedly enjoyed his frequent visits in the capacity of a Governor and, throughout the whole period, as a most regular and valuable member of the Council of the Medical School. We loved having him with us and felt that his presence was of immense value. Jock was not a vocal committee man, but we knew that he quietly assessed all that was said and that if he was dissatisfied on any matter he would be certain to ask for enlightenment or express his disapproval. His counsel, if perhaps because it was seldom expressed, was always wise and no thoughtless word ever seemed to escape him. His ingrained determination to be completely kind, fair and honest could be truthfully said to epitomize Jock's character. It was ever present in his life both at home and in his work. He was the most approachable of men and his good judgment must have deterred many from making serious mistakes. The three characteristics mentioned above entirely governed any decision he made in his work, with the result that his patients soon came to know they were in the hands of a man they could respect and for whom they rapidly gained a great affection. If Jock had a love for his hospital, it was shown throughout his life by a meticulous devotion to duty. This did not pass unobserved by the many who served under him and he started a tradition that will last through generations. I well recall that he would consider leaving any of his hospital work

only in the event of a real emergency. His teaching was sound, simple and easily followed. He realized that the majority of his audience would enter general practice, and from his personal knowledge of the family doctor's life he was able to give first-class instruction on the troubles likely to occur and on what action should be taken.

Jock's life was not all work—far from it. He and Mrs. Jock had a goodly family of five sons and one daughter and his first love was his home and its activities. Hedley hospitality was proverbial, and many, especially those who were cricketers, will never forget the happy hours, or days, that were spent at Cobham. Jock had also a delightful sense of humour, which was never tainted with sarcasm. The worst he could ever raise against anyone for whom he obviously had no liking, and less respect, was the remark, "Of course, the man's a perfect ass".

The death of Mrs. Hedley in 1945 was a blow, the magnitude of which was known only to a few intimate friends, and the last few years could be described as an interim period devoted to tasks which he considered might be of some use and of help to others.

Jock will be sadly missed.

ARTHUR J. WRIGLEY.

ROYAL COLLEGE OF OBSTETRICIANS AND GYNAECOLOGISTS

Andrew M. Claye, Esq., M.D., F.R.C.S., F.R.C.O.G.
(*Professor of Obstetrics and Gynaecology at Leeds University*)

has been elected President of the College.

THE 1957 LONDON MEDICAL EXHIBITION

THIS takes place from 18th to 22nd November at the Royal Horticultural Hall, Westminster. It will be officially opened at 11.30 a.m. on 18th November, by Sir Bennett Hance, *K.C.M.G.*, *K.C.I.E.*, *O.B.E.*, M.D., F.R.C.S.(Ed.), Medical Adviser to the Secretary of State for Commonwealth Relations.

Some one hundred and twenty leading manufacturers will be exhibiting drugs and medical specialities; surgical, medical and hospital apparatus and instruments; technical literature; research apparatus and, in fact, the widest possible range of medical and allied products.

A programme of the latest medical films, which will be showing at all times during the exhibition, will provide professional visitors with much interesting and important information.

Visitors may obtain excellent meals in the comfortable Exhibition Restaurant on the lower ground floor, and refreshments of various kinds are available in the building.

Professional men and buyers from overseas are welcome, and invitations may be obtained by writing to: The Organizers, London Medical Exhibition, 194–200 Bishopsgate, London, E.C.2, England. Visitors without entry tickets are requested to produce professional identification.

SEVENTH INTERNATIONAL CANCER CONGRESS, LONDON, 1958

THOSE planning to attend the 7th International Cancer Congress, which will take place at the Royal Festival Hall, London, from 6th–12th July, 1958, are reminded that enrolment forms must be received at the Congress Office (45 Lincoln's Inn Fields, London, W.C.2) *by 1st January, 1958* if a late fee is not to be incurred. Registration forms may be obtained from the Secretary-General at that address.

REPORTS OF SOCIETIES

GLASGOW OBSTETRICAL AND GYNAECOLOGICAL SOCIETY

FEBRUARY 1957

A meeting of the Glasgow Obstetrical and Gynaecological Society was held in the Royal Faculty of Physicians and Surgeons on 20th February, 1957. The President, Professor D. F. Anderson, was in the Chair.

Professor H. C. McLaren gave an address on

CARCINOMA IN SITU

He said that carcinoma *in situ* may well be called the "snark" syndrome, since none of us are quite sure how it is to be found and once found what we should do with it!

In 1952, the Professorial Unit in Birmingham set out to apply the technique of cytology to the out-patients' service, omitting only very occasional patients from the screen (McLaren, Taylor and Attwood, 1956). The method of vaginal cytology was selected as being the most practicable method of apparently matching any other technique in its efficacy. The first task was to establish the technique and, with the help of colleagues in U.S.A., the senior technician, Miss M. E. Attwood, was trained as a cytologist and in due course she created a small team of technicians who were able to screen an increasing number of patients. The technique involving the recognition of cancer cells in vaginal smears rests with the technicians.

The lecturer then went on to define the uses of cytology. He emphasized that invasive carcinoma of cervix or corpus practically never requires a cytologist to reach a diagnosis although a confirmatory smear is of value. The main purpose of cytology is to discover cases of carcinoma *in situ* (of the cervix) in clinically normal cases.

The Cost of a Cytology Service

The effort in discovering a single case of carcinoma *in situ* is considerable. For example, just over 1,000 smears have to be screened to discover 3 examples of carcinoma *in situ*. A greater "harvest" of carcinoma *in situ* was expected but with experience of 6,000 smears and a huge number of hours at the microscope only a few cases have been discovered. The important point is not simply that cytology is expensive in money, it is very expensive in time and effort.

Results

	A 1952–4	B 1954–6
Total patients	2,250	2,000
Carcinoma *in situ* (typical) Carcinoma *in situ* (atypical)	38	6

Treatment of Carcinoma In Situ

Petersen (1955) reported that over a period of 8 years 27 per cent of his series of carcinoma *in situ* had developed invasive carcinoma. The obvious question which has to be answered at the outset of any study is an ethical one, namely, is it justified to leave carcinoma *in situ* untreated?

To diagnose carcinoma *in situ* a vaginal smear is followed by histological confirmation. Such confirmation may be obtained from a small punch biopsy from one or two areas on the portio vaginalis and some clinicians would be content with this, excluding co-existent *invasive* carcinoma by means of an endocervical curettage and endometrial curettage.

In Birmingham, however, it is considered necessary to undertake a ring biopsy as well as endocervical and endometrial curettage in order to exclude the definite risk of co-existent invasive carcinoma. But is a ring biopsy a therapeutic measure? It usually is, and 13 cases of carcinoma *in situ* were treated simply by ring biopsy. The ring biopsies were cut in the shape of a dunce's cap to include the squamo-columnar junction, most of a large area of the portio vaginalis, and at least the lower part of the cervical canal. These were subjected to serial sectioning, the final opinion on pathology resting with Dr. C. W. Taylor, Director of Pathology, Birmingham and Midland Hospital for Women.

A necessary condition to this form of investigation-plus-treatment was that each case must be followed up at regular intervals by clinical and cytological methods for an indefinite period. Professor McLaren pointed out that the total follow-up period for the Birmingham cases was much too short for any set of working rules to be evolved which might assist the clinician in charge of the case of carcinoma *in situ*. Nevertheless, experience to date suggested that a conservative attitude was justifiable, especially in the younger woman, e.g., a woman desirous of children, provided a meticulous follow-up was feasible. In a woman aged 40 and over, hysterectomy with its very low morbidity and almost negligible mortality was obviously the safest and best treatment.

Some of the patients treated in the Birmingham series might be considered to have been overtreated by a Wertheim operation although this information was only obtained in retrospect following a complete study of the operative material. A survey of the important series in the literature of treated cases of carcinoma was presented which emphasized the overwhelming opinion that radical treatment by surgery or full irradiation was accepted as the only safe method of treatment of carcinoma *in situ*. The Birmingham experience was, of course, very small in comparison but to date, in 19 cases of carcinoma *in situ*, 6 have been subjected to surgery and 13 to simple ring

biopsy and careful follow-up using both clinical and cytological methods.

Finally, it was suggested that if a widespread screening project were considered in Glasgow or Birmingham, it would be wise to form a Committee for the study of carcinoma *in situ* so that all knowledge could be pooled with the object of working out the natural history of carcinoma *in situ*.

Summary

Provided a full ring biopsy is taken as well as careful endocervical and endometrial curettage, the Birmingham experience suggests that a conservative line of therapy is justifiable. The question is, of course, *sub judice* but a plea was made for careful consideration of every case by a clinician in consultation with the cytologist and pathologist.

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NORTH OF ENGLAND OBSTETRICAL AND GYNAECOLOGICAL SOCIETY

April 1957

A Meeting of the North of England Obstetrical and Gynaecological Society was held in Leeds on 26th April, 1957. The President, Mr. F. Stabler, was in the Chair.

Mr. H. A. Kelsey reported a case of

Pregnancy Associated with Diabetic Nephropathy

(This article appears on page 735 of this issue)

Discussion

The President congratulated Mr. Kelsey on steering the patient through such perils, but doubted if the risk should have been taken. He also recalled the case of a patient who developed fits, albuminuria, papilloedema and later blindness, at the 26th week of pregnancy. She was delivered by Caesarean section 4 weeks later, and the baby, who weighed 2 pounds 13 ounces, did well and the patient's eyesight returned.

Mr. T. B. FitzGerald commented on the courage required to try to save so tiny a child. There are so many babies that die *in utero* at the 35th week of pregnancy, that it is necessary to attempt delivery earlier.

Dr. D. Keith described a case of

Vaginal Delivery of Full-time Conjoined Twins

(This article appears on page 726 of this issue)

Discussion

The President asked if after delivery of the head and shoulders some form of embryotomy would not have been easier than bringing down the legs.

Mr. T. F. Redman enquired about the mechanism of delivery when the union was higher up.

Mr. D. H. Lees had delivered thoracopagus twins, but he did not know how it was done. After delivery of the first head the second was found in the vagina. The patient had very strong pains and the twins were delivered together with the head of the second at the level of the chest of the first. The babies weighed 8½ pounds and lived 4 days.

Mr. W. Hunter had had a case under his care, but expulsion of the first twin was soon followed by the second. On X-ray the heads may not be at the same level, but, if the two foetal skeletons form a symmetrical pattern, conjoined twins should be considered. A similar pattern may be found if a double uterus is present.

Mr. B. Williams asked what sex was given at registration?

In his reply Dr. Keith said he had not known whether to notify the birth of one or two babies, and, as the sex was not known, they were called female. He approached destructive operations with trepidation, and in fact it had proved easy to bring down the limbs.

Professor C. S. Russell, Miss M. G. Coyle and Dr. C. G. Paine read a paper on

The Pregnanediol Excretion in Normal and Abnormal Pregnancy with Observations on Placental Histology

(This article appears on page 649 of this issue)

Discussion

The President congratulated the authors on this important work. Not many of the tests of placental function can be relied on, but Miss Coyle had developed one that gave a clear indication of placental activity. The exposition on the changes associated with placental ageing and disease had been clear. He thought that it would be valuable if there were an easy test on the serum as the end-product in the urine may not be a reliable reflection of the progesterone in the circulation.

Mr. G. W. Theobald offered his congratulations to the Sheffield school. Pregnanediol excretion was normal in some cases of eclampsia and yet in some placentae there were specific changes. He thought pregnanediol excretion was of value in prognosis, but questioned whether it gave real evidence of placental function.

Mr. T. B. FitzGerald said that on looking through his records he had not been able to find an absolute correlation between placental function and foetal loss in toxaemia cases. In the fulminating case there may be no placental deficiency.

Mr. P. Malpas commented on the fall in pregnanediol excretion that occurred in normal pregnancy.

Professor Russell in reply stressed that it was difficult to collect a 24-hours specimen of urine accurately. Moreover, to do the assay properly was difficult, as was also the clinical application. It is important to move cautiously and not perform a large number of Caesarean sections because of low readings. Yet if rupture of the membranes was considered a high pregnanediol value would not make you hold your hand. In postmaturity the results were the same as in diabetes.

Dr. Paine questioned if the picture would be more accurate using serum. The values of pregnanediol excretion can only be related to syncytial function, which may be reduced by degeneration or infarction.

HOSPITAL REPORTS

JOHN S. TOMKINSON, M.B., F.R.C.S., M.R.C.O.G.

A REPORT ON SOME ASPECTS OF THE MATERNITY SERVICES IN THE SOUTH WESTERN HOSPITAL REGION OF ENGLAND, MARCH, 1957

THIS enquiry was initiated and controlled by the South Western Region Hospital Board; the Nuffield Provincial Hospitals Trust approved the scheme and was responsible for the cost. The main objectives were:

(1) To assess the adequacy of the services provided by general practitioners, hospitals and the local health authorities;

(2) To study the reasons for deciding whether confinements should take place in the home; and

(3) To compare the merits and cost of home and hospital confinements.

Mr. A. J. McNair was the Director of the Committee and Mr. H. L. Shepherd the steering committee Chairman. The committee of five was representative of general practitioners, medical administrative and academic interests in the region, with the help of a statistical adviser.

The first three chapters of the report are introductory, dealing with the evolution of Maternity Services throughout the country, the objects and scope of the survey and the survey method itself. A questionnaire was drawn up and the questions put by health visitors to mothers six or eight weeks after delivery. In this way, it was hoped, a frank opinion would be obtained as to the satisfaction the maternity service gave to the public. The questionnaire consisted of 52 items, many of them sub-divided; details were required about the present and previous children, the antenatal care (particular attention was paid as to its quality, such as "was blood taken from a vein in your arm for examination in a laboratory?" "were you weighed regularly?", "were you given instruction in relaxation exercises?"), the confinement, the postnatal period and baby feeding, the mother and her work, the husband, maternity benefits and the home.

The number of births notified in a three-week period of May, 1955 was taken as yielding a statistically representative sample; this gave a total of 2,499, of which 2,431 were successfully interviewed. One maternal death occurred; the other failures were due to moving home, refusing to co-operate, mental illness and the like.

A hospital delivery occurred in 62·2 per cent of cases; 1,020 booked for home confinement but 147 were transferred to hospital during pregnancy or labour, whereas of 1,404 booked for hospital confinement 42 had their babies at home (only in one instance because the hospital was full). Of all the mothers interviewed, 82·4 per cent were both booked and confined in accordance with their own preference and of these 88·4 per cent stated that at any future confinement they would like to be confined in the same place. Only 2·6 per cent of mothers were confined at home whilst not preferring it and this would appear to indicate that in the South Western Hospital Region the customer is satisfied in a high degree. The report compares the 62·2 per cent of women who had a hospital confinement with the committee's estimate of 70 per cent who needed hospital accommodation in the light of present-day obstetric opinion (in this country).

That there was a considerable variation in the importance attached to different items of antenatal care is shown in a table (No. 7) indicating the percentage of primigravidae receiving them; for instance, 97 per cent provided a specimen of urine every time, but only 35·5 per cent had a chest X-ray and merely 32 per cent had instruction in mothercraft. Reviewing all mothers, the committee found that 81·8 per cent of those in hospitals received good care, whereas 59 per cent and 67·5 per cent of patients delivered at home or as paying patients in hospital or nursing home respectively, received supervision of an equal standard. No correlation was found between poor antenatal care and foetal or infant mortality; it is possible that a larger series might indicate a connexion and in any case the standard of "good" care adopted by the committee refers to the quality and not the number of attendances.

No less than 12·7 per cent of all the patients suffered at some time from albuminuria, raised blood pressure, marked oedema or other sign which placed them in the "toxaemia" group; and 8·7 per cent of the babies in this category were stillborn or died (the perinatal mortality for all deliveries being 4·1 per cent), the infant loss being lower in hospital than at home.

The chapter on the relief of pain in childbirth mentions with commendable pride that of the 707 midwives employed in the domiciliary service in the Region, all but one had a certificate for the administration of gas and air. Out of the women interviewed, 91·6 per cent had analgesia, 2·3 per cent were offered but refused analgesia and 6 per cent were not offered analgesia. Only 2·8 per cent of mothers confined at home and 5·2 per cent of those delivered in hospital complained that the pain relief was given late or inadequately.

When commenting on infant feeding the report mentions the favourable results that have been obtained by various investigators elsewhere in the country who have followed Dr. H. Waller's teaching, but the rather startling conclusion was obtained from the figures of the present survey that "the proportion of home delivered

primiparae still breast-feeding (wholly or with complement) was higher among those who had not than among those who had received mothercraft training". As this conflicts with the findings of others it may indicate that the mothercraft training as given does not stress sufficiently the preparation during pregnancy as stressed by Waller.

The short chapter on the postnatal examination is full of common sense, underlining the importance of assessing the general health of the woman. Many will applaud the opinion that no scheme of "Maternal Welfare" is complete without advice on contraception for those mothers who need it.

This report will recompense those who study it. The survey had been planned with great thought and obviously the compilation of the minutiae has taken up a lot of the time of midwives and health visitors. To them, to the committee responsible for the report, to the Regional Hospital Board and to the Nuffield Provincial Hospitals Trust, we offer our thanks.

CLINICAL REPORTS FOR 1955 OF THE MATERNITY HOSPITALS OF THE TEACHING HOSPITALS BOARD OF THE UNIVERSITY OF CAPE TOWN

(1) The Peninsula Maternity Hospital; (2) The Mowbray Maternity Hospital; (3) The New Somerset Hospital, Shipley Ward; (4) The St. Monica's Maternity Hospital

It is not possible to comment fairly upon reports unless there is some indication in a preamble of the type of patient admitted. This is obviously important in the case of reports from hospitals receiving patients greatly divergent in racial characteristics, economic status and health. It may even be misleading to use figures from such reports for comparison with other hospitals. It would appear that in fact this has happened by the use of the information from the reports of this group of hospitals (vide letter from Dr. L. Resnick, *Brit. med. J.*, 20th July, 1957, page 162, "Post Maturity"); this letter indicates that one hospital admits almost entirely non-white and largely non-booked patients dealing with medical complications of pregnancy such as the toxaemias, eclampsia, diabetes, cardiacs, etc. In the absence of information about the working background of each hospital any conclusions drawn and comparisons made would be valueless.

THE CLINICAL REPORT OF THE CHELSEA HOSPITAL FOR WOMEN FOR THE YEAR 1954

The pattern of previous years has been followed in the clinical report and reports from the cancer clinic, pathology department and the endocrine laboratory unit. Non-malignant cases accounted for 2,569 admissions (no deaths occurred in this group) and malignant cases totalled 129 with 35 malignant cases re-admitted. Sixteen deaths occurred during the year, all of them suffering from malignant disease; there is a special report on these cases in which a summary is given about each patient. These are of value and it would make the report as a whole more enlivening if cases of special interest could be abridged similarly.

The most important section is the cancer report, which deals with all malignant cases seen in 1954 and includes a record of cancer of the cervix from 1933 to 1954. Since 1944 a Joint Clinic has been held by a surgeon of the hospital and a radiotherapist on the staff of the neighbouring Royal Marsden Hospital, but not all patients have their treatment planned by this clinic as some are treated entirely by a surgeon without reference to the radiotherapist. Although the number of cases having received treatment is small, the 5-year survival rate of those patients who have had their treatment planned by the joint clinic appears to be substantially better than the remainder.

THE CLINICAL REPORT OF THE MATERNITY UNIT, WEST HILL HOSPITAL, DARTFORD, KENT, FOR 1955

Since the introduction of annual reports in 1952, this unit has admitted an increasing number of booked and non-booked patients. There is no mention of the number of beds in the unit, but during 1955 a certain number of beds were allocated for general practitioners, who did not have to satisfy any particular standard of need for admission. There is no index to the report.

During the previous few years there has been a steady fall in the incidence of morbidity and also in the foetal mortality of the booked cases; in 1955 the stillbirth rate per 1,000 total births was 20·1 and the neonatal death rate was 24. Only one mother has died in the unit since 1952, out of a total of 4,972 cases; she was an emergency admission with severe pre-eclampsia who died of renal failure. This is a praiseworthy record of which the unit should be proud. Only one case of special interest is mentioned briefly, that of a woman who passed a foetus in April and in November of the same year had a spontaneous delivery of a live infant weighing 5½ pounds.

BOOK REVIEWS

"A Textbook of Gynaecology." By K. M. MASANI, M.D., F.R.C.S., F.I.C.S. Second edition. Pp. xvi+775, with 276 figures. Popular Book Depot, Bombay, 1957. Price Rs. 25.

THE warm welcome extended in this Journal (October, 1954) to the first edition of this textbook from India has obviously been widely shared. The result is the appearance, within 3 years, of a second edition, wholly revised, partly re-written and some 100 pages longer. The illustrations and the composition have both been improved, but the English is still occasionally stilted and errors in the spelling of some proper names persist. A brief historical note now introduces each chapter and a list of references is appended to most sections. These references, however, do not cover all the authors quoted in the text, nor are they always set forth in the generally accepted style.

The teaching is, as before, concise and modern, with the section on malignant growths, contributed by Dr. E. J. Borges, outstanding. "Masani" is likely to become the standard gynaecological textbook for students and graduates in India and its neighbouring countries.

"Advice to the Expectant Mother." By Emeritus Prof. F. J. BROWNE and Prof. J. C. MCCLURE BROWNE. Eleventh edition. Pp. 48. E. & S. Livingstone Ltd., Edinburgh and London, 1957. Price 1*s*.

"Relaxation and Exercise for Natural Childbirth." By HELEN HEARDMAN. First edition, ninth reprint. Pp. 32. E. & S. Livingstone, Ltd., Edinburgh and London, 1956. Price 1*s*.

EVEN where the education of the pregnant woman is of a high standard, the spoken word is best reinforced by the written word, to be studied at leisure at home. These two inexpensive booklets are of acknowledged value in this field. Both are written in simple direct style, although occasionally a word appears which may be outside the vocabulary of the average lay reader.

For the eleventh edition of Prof. F. J. Browne's pamphlet, first published in 1926, Prof. J. C. McClure Browne has become joint author, while Dr. J. P. M. Vizard has revised the chapter on breast-feeding and care of the baby. The benefits of antenatal care are here and there presented in a way that may, unintentionally, make the nervous primigravida even more apprehensive (e.g., in regard to breech presentation), but the carrot and the whip are perhaps complementary stimuli. On the whole, however, this booklet maintains an admirable balance between insufficient information and too much detail.

Helen Heardman's pamphlet is based on the principles of Grantly Dick Read, and sets forth relaxation techniques and exercises and their application in the various stages of labour. The addition of a short chapter on postnatal exercises would be a welcome addition to this most valuable twelvepennyworth.

"Trophoblastic Growths. A Clinical, Hormonal and Histopathologic Study of Hydatidiform Mole and Chorionepithelioma." By J. SMALBRAAK, M.D. Pp. xii+342, with 66 figures. Elsevier Publishing Co., London, 1957. Price 72*s*.

STUDY of the rare tumours which arise from trophoblast presents many fascinating problems to clinician and pathologist alike which necessitates close co-operation and thus stimulates healthy controversy and constructive criticism. Dr. Smalbraak, in this well presented and beautifully illustrated volume, reviews the most important contributions to the literature on the subject and adds a comprehensive clinical, hormonal, and histopathological survey of 74 hydatidiform moles and 17 cases of chorionepithelioma seen at the University Clinic, Utrecht, between 1926 and 1952.

Included in the historical review is the remarkable tale of the demise of the Countess of Henneberg in 1276 from a presumed hydatidiform mole and of the astonishing feat of her priest in sexing all the vesicles into 365 "children".

The theories propounded to explain the aetiology of trophoblastic tumours offer no real light on the subject. Nevertheless, they make entertaining reading.

Biological tests are less reliable in diagnosis than is commonly supposed. Occasionally they remain positive, without explanation, for many weeks or even months after the complete expulsion of a mole. An increasing titre should, however, be regarded as an indication of increasing vitality of trophoblastic tissue somewhere within the body. In chorionepithelioma, also, tests are sometimes persistently negative, or remain persistently positive after treatment in the absence of any demonstrable lesion. In spite of their limitations, however, bio-assays remain the most reliable aids to diagnosis and of all the methods available the Aschheim-Zondek reaction still remains supreme.

Lesions emanating from molar tissue are divided according to the suggested classification of Hertig and Sheldon into four grades of malignancy; namely, syncytial endometritis, chorionepithelioma *in situ*, chorioadenoma destruens and chorio carcinoma, but only the latter gives a poor prognosis.

Routine curettage is recommended after all spontaneous, or induced expulsion of moles. Occasionally the neoplastic tissue may be out of reach of the curette deep within the myometrium and there is always a tendency to over-estimate the grade of malignancy from curettings. In proven cases of invasive mole local excision is adequate, whether the growth occurs in the uterus or at a distance. Hysterectomy should be reserved for cases of

malignancy only and the ovaries should be conserved since there is evidence to support the view that oestrogen inhibits the growth of trophoblast.

Chorionepithelioma occurs at the extremes of reproductive life and occasionally even during pregnancy. Rarely it presents clinically through secondary deposits in lungs or brain and successful lobectomy and craniotomy are reported. There is a complete lack of unanimity regarding treatment but the author concludes that the method of choice is surgery supported by general measures to restore vitality. Total hysterectomy is the usual operation, ovarian function being conserved. Vaginal deposits are best cauterized to reduce the risk of severe haemorrhage. Massive dosage oestrogen therapy is advocated for inoperable cases and should be controlled by serial hormone assays. There is no proof of any beneficial effects from the use of irradiation, nitrogen mustard, radio-active phosphorus or pituitary-inhibiting drugs.

It seems a tragedy that half the bibliography and part of the Dutch summary should fall a prey to the bookbinder's guillotine. It is to be hoped that this serious handicap is still remediable, for the volume is otherwise an invaluable and up-to-date work of reference on trophoblastic growths, benign and malignant.

"Martius' Gynaecological Operations." Translated and edited by MILTON N. MCCALL, M.D., F.A.C.S., and KARL A. BOLTEN, M.D. Pp. xiv+405, with 450 illustrations. J. & A. Churchill, Ltd., London, 1957. Price £7 5*s*.

THIS is the second English language translation of Professor Martius' well-known German text on operative gynaecology and covers the seventh edition which was published in Göttingen in 1954. The American editors have done extremely well to reduce it to its present size without loss of individuality.

The outstanding feature of the book as a whole is the masterly use of the surgeon's pen and the artist's brush to describe and illustrate with great simplicity even the most complicated procedures, including Wertheim's hysterectomy and radical vaginal hysterectomy. While some may dispute small anatomical or technical points one cannot fail to be profoundly impressed with the ease with which anatomy is built up into operative techniques. Often the same objective is approached equally effectively by different routes and methods. Occasionally the usual form is reversed and operative procedures made to illustrate the anatomy of an area. This is particularly evident in the use of the inguinal sterilization operation and Alexander-Adams procedure to display the inguinal canal—an important, but frequently neglected area.

A rather nostalgic note is struck in the chapter dealing with chronic inflammatory diseases. Advances in antibiotic therapy have made this a resting place for "old crocks". Buttner's defundectomy, Kelly's bisection subtotal hysterectomy and Faure and Döderlein's bisection total hysterectomy are now almost, if not entirely, obsolete. Their inclusion is justified however if only for sentimental reasons.

The author expects criticism of the revised chapter on sterility and sterilization, but one cannot fail to compliment him on his excellent success rate of 54 per cent following salpingolysis or salpingostomy for hydrosalpinx. Also for his unbiassed presentation of various operations for ovarian and tubal implantation with an added note of warning that the successful results hardly outweigh the risks involved.

Professor Martius and his staff have a special interest in the treatment of all forms of urinary incontinence and it is, therefore, not surprising that numerous techniques of their own are included in addition to the conventional types. Best known is the bulbocavernosus fat flap operation which can be used to advantage in treating both stress incontinence and urinary fistulae.

The overall excellence of this presentation, which covers most of the operative procedures used in gynaecology, is such that any point of criticism will seem quite trivial. Vault prolapse and radical vulvectomy are two important topics dismissed in a few words. It is also difficult to justify the use of laminaria tents to dilate the cervix prior to a curettage, especially when their use also involves a second anaesthetic.

There is no doubt that this book will vie with the best British texts as a work of reference for the surgeon in training. No book can replace training and experience in the operating theatre, but this book will undoubtedly add polish.

"A Practical Handbook of Midwifery and Gynaecology." By W. F. T. HAULTAIN, *O.B.E.*, *M.C.*, F.R.C.P.Ed., F.R.C.S.Ed., F.R.C.O.G., and CLIFFORD KENNEDY, F.R.C.S.Ed., F.R.C.O.G. Fifth edition. Pp. x+410. E. & S. Livingstone, Edinburgh and London, 1957. Price 30*s*.

IN this fair-sized but inexpensive book from the Edinburgh school, the emphasis, especially in the obstetrical section, is on the practical aspect. The chapter on normal labour is outstanding in this respect, while a breath of Scottish air is reflected in the advice to the pregnant to wear warm underdrawers to prevent chilling. But some of the recommended practices are not in accord with general usage today. Thus external pelvimetry is performed as a routine, pituitrin is given in late pregnancy and labour, forceps may be applied to the impacted breech, and one of the rules given for the delivery of cardiac cases is "allow fairly free bleeding during third stage, as it relieves tension on heart". The use of forceps in secondary uterine inertia is regarded as absolutely contra-indicated, while Caesarean section finds no mention as a possible form of treatment in persistent mento-posterior or in a shoulder presentation diagnosed in labour.

In the comprehensive section on gynaecology, the well-balanced chapter on hormone therapy and the logical discussion of amenorrhoea and its investigation stand out. Diseases are considered largely under the heading of individual organs, and this makes it difficult for the reader to obtain a full picture of endometriosis and genital tuberculosis. The standards given for male

fertility are much too high, for sterility is dogmatically declared if the sperm count is below 60 millions per c.cm., the percentage of abnormal forms above 25, or the proportion of non-motile sperms more than 15 per cent (after an unspecified interval).

While facile writing makes reading and assimilating more easy for some, a text in tabulated form, such as this, appeals to many with orderly minds as well as to those seeking a quick reference to the possible solutions to a clinical problem. The latter will find this book very useful, but would benefit from a more detailed index.

"A Pocket Obstetrics." By ARTHUR C. H. BELL, M.B., B.S., F.R.C.S., F.R.C.O.G., Hon.M.M.S.A., Obstetric Surgeon, Westminster Hospital; Surgeon, Chelsea Hospital for Women; Consulting Surgeon, Queen Charlottes Hospital, London. Fourth edition. Pp. 156, with 15 illus. J. & A. Churchill, London, 1957. Price 10*s.* 6*d.*

To compress the whole of obstetrics into less than 160 small but readable pages is such a feat that to offer any critical comment seems a trifle ungracious. The new edition of this handy pocketbook has been brought up to date, with afibrinogenaemia and retrolental fibroplasia among the added subjects, but further revision, even at the expense of adding a few more pages, might be considered for the next edition. Some account of local analgesia for forceps might be introduced and the problems of postmaturity considered. The modern shift in emphasis from albuminuria to hypertension as the most important feature of pre-eclampsia might be more strongly stressed and the subject of essential hypertension complicated by pregnancy be separately discussed. It is, however, in relation to the third stage of labour that most questioning of the text might arise. It might be advantageous in this respect to differentiate between third stage bleeding and true post-partum haemorrhage; to advise exploration of the uterus for the latter if persistent or recurrent; and to indicate that the delivered secundines should always be carefully inspected. The risks of manual removal of the placenta are perhaps exaggerated, and it may not be accepted generally today that this operation should be avoided or deferred for some hours in the patient who is not bleeding at the moment but is in poor condition from third stage haemorrhage, or who has a retained placenta after a long labour.

Obstetrics, however, is still an art and not an exact science, with room for differences in management, and this book remains a helpful pocketful for the practitioner and the final year student.

"Munro Kerr's Operative Obstetrics." By J. CHASSAR MOIR, M.A., M.D., F.R.C.S.E., F.R.C.O.G., Hon.LL.D. Sixth Edition. Pp. 1008, with 404 illustrations. Baillière, Tindall and Cox, 1956. Price 105*s.*

THE first edition of *Munro Kerr's Operative Obstetrics* was published almost 50 years ago, when its author was still a young man and it has maintained its position as the standard reference book on the subject in Britain ever since. Professor Chassar Moir who was joint author of the fifth edition has now taken over the full responsibility for the latest edition. He has accomplished with credit the difficult task of retaining what was best in the old edition and adding new material to bring the present volume up to date. This has involved a great deal of reading since there are very many new references. It is very difficult to write a book which is suitable for all parts of the world since the obstetrical problems vary so much with the stage of development of the country in question. Some complications of pregnancy and labour which have almost disappeared from Britain may still be relatively common in the underdeveloped countries. It is doubtful, however, if enough of the out-of-date material has been discarded. For example, it seems unnecessary to advise that the external pelvic measurements be taken routinely with calipers. In dealing with surgical induction of labour the relative risks of sepsis following artificial rupture of the membranes and the introduction of bougies is discussed in detail although the latter method is more seldom used but the possible risks of infection of the foetus following artificial rupture of the membranes is not mentioned. The use of the pitocin drip is not described. Some of the statistical tables are out of date. For example, it seems of doubtful value to retain tables showing stillbirth rates in cases of contracted pelvis occurring in the Glasgow Maternity Hospital in the years 1930–33. It also seems a little surprising that routine X-ray pelvimetry should be advocated prior to labour in all primigravidae. Not more than 1 per cent of primigravidae in this country require to have Caesarean section because of disproportion, so that disproportion is becoming uncommon. In addition recent publications have drawn attention to the comparatively large amount of radiation received by the foetal gonads when the brim measurements are being taken.

In general it seems a reasonable conclusion that much more of the out-of-date material could have been omitted and more space given to a more critical review of the newer aspects of operative obstetrics. The production of the book is excellent and some of the X-ray photographs are quite outstanding. Altogether this remains a most authoritative postgraduate textbook of operative obstetrics.

"Human Cancer." By MAURICE M. BLACK, M.D., and FRANCIS D. SPEER, M.D., F.C.A.P. Pp. 273, with 34 figures. The Interscience Publishers, Ltd., London, 1957. Price 57*s.*

IT takes courage and enterprise to add yet another book on cancer to the already existing literature on the subject, the more so as the authors have confined themselves to 263 pages of a pocket-size edition. It also takes skill and a great understanding of the subject matter to squeeze the essential data regarding human cancer into such a small handbook. Despite the unavoidable drawbacks of brevity, the most regrettable of these being dogmatism, the sparseness of illustration and a probably deliberate omission of patho-histological descriptions, the authors must be congratulated on having achieved their aim and on having produced a very readable little book which will delight the student and the novice in this field.

The subject is discussed in five general chapters on cancer detection, human carcinogenesis, biological behaviour, biochemistry and chemical and radiation therapy, followed by thirteen chapters arranged according to the various anatomical sites of primary malignant growths. The five theoretical chapters provide a wealth of information on current trends in cancer research and will certainly whet the appetite to acquire deeper knowledge and to study the controversial points in greater detail. The reader will be encouraged and helped in this endeavour by the extensive lists of pertinent literature appended to each chapter.

This little volume most certainly deserves a warm recommendation as an excellent introduction to the problem of human cancer.

Erica Wachtel

"Pelvimetry." By HERBERT THOMS, M.D. Pp. 120, with 45 illustrations. Cassell & Co., Ltd., London, 1957. Price 37*s.* 6*d.*

DR. HERBERT THOMS ranks high amongst the pioneers of the modern era of obstetric practice for his valuable contributions in the field of pelvic radiography over a period of 30 years. In this slim volume he presents his basic thesis in a simple, effective style which conveys strong conviction. Technical minutiae and detailed discussions, which already appear in the original papers, are not duplicated. A survey of the whole subject from early pelvic development, through the influence of environment during the period of growth, to the effect of pelvic shape and size on the course of labour, is thus made possible and used to reinforce his plea for the universal application of pelvic radiography during pregnancy particularly by the single film screening survey method.

The emphasis throughout is on pelvic structure and on assessment of the cephalo-pelvic relationship before the onset of labour. It might be argued that a more objective assessment during labour, even without accurate mensuration, permits a simultaneous appraisal of both structure and function. Such a trend of thought seems to be gaining favour. Nothing, however, can belittle Dr. Thoms' outstanding contributions which have, in turn, stimulated further progress.

"Practical Gynecology." By WALTER J. REICH, M.D., F.A.C.S., F.I.C.S., and MITCHELL J. NECHTOW, M.D., F.A.C.S., F.I.C.S. Second Edition. Pp. xviii+ 648, with 284 illustrations. J. B. Lippincott, Co., Philadelphia, 1957. Price £5.

FOR the second edition of this popular American text the authors have revised the whole work and added nine new chapters. These latter include subjects of topical interest such as exfoliative cystology, early diagnosis of ovarian carcinoma, paediatric and geriatric gynaecology and radiation therapy. Paradoxically, the opening chapter on "Psychosomatics of Gynecology" is the least "practical", possibly because the whole subject is still in its infancy. A discussion of the role of the male in gynaecology serves to emphasize his presence as a shadow looming in the background of many gynaecological problems, especially those of a psychosomatic nature.

Once opened this book is difficult to put down for it presents an authoritative approach to every subject, with colourful clinical anecdotes woven into the text to enhance the variety and to drive home a point more effectively. Full use is also made of the photographer's art, both in colour and black and white. It is remarkable to find no significant point of dispute in such a comprehensive book, but such is the case.

It only has one fault, namely the price, but even allowing for the present adverse rate of exchange, it is worth every cent. As an accurate and up to the minute survey of the American scene in gynaecology it cannot be challenged.

SECOND WORLD CONGRESS OF THE INTERNATIONAL FEDERATION OF GYNAECOLOGY AND OBSTETRICS

ANNOUNCEMENT

THE International Federation of Gynaecology and Obstetrics was founded in Geneva in 1954 where it held its First World Congress. Meeting every four years, according to its Constitution, the International Federation chose Montreal, Canada, as the site of its Second World Congress, from 22nd to 28th June, 1958. All scientific sessions, scientific exhibits, and moving pictures will be held in the newly-built Queen Elizabeth Hotel. The main features will be plenary conferences with invited guest speakers, round table discussions, and free communications. Information and registration forms may be obtained by writing to the Montreal Committee, Second World Congress, International Federation of Gynaecology and Obstetrics, 1414 Drummond Street, Suite 220, Montreal 25, Quebec, Canada.

REVIEW OF CURRENT LITERATURE

CONTENTS

	REF.
PREGNANCY	347
LABOUR	362
LACTATION	375
INFANT	376
OBSTETRIC OPERATIONS	385
GYNAECOLOGY	386
Infections of the Reproductive Organs	392
New Growths of the Reproductive Organs	396
Operations	412

PREGNANCY

347. **Factors Affecting Relaxation of the Pelvis During Normal Pregnancy, Delivery, and the Puerperium.**

By C.-E. JOHANSON and P. A. JÄRVINEN. *Acta obstet. gynec. scand.*, **36**, 179–193. 1957. 11 figs. 36 refs.

Working at the First and Second Gynaecological Clinics of Helsinki University the authors studied radiographically the mobility of the pubic symphysis during normal pregnancy and delivery, with special attention to both widening and longitudinal displacement. Three groups of women were studied: (*i*) 98 were examined 2 to 3 days after delivery, and 43 of them 2 years later to ascertain the permanence of the post-partum changes; (*ii*) On 45 women radiographs were taken 1 to 2 weeks before the expected dates of delivery, and again 2 to 3 days after delivery; (*iii*) Sixteen nulliparous, non-pregnant women of similar age groups (16 to 45 years) were examined by the same radiological technique as a control series.

The incidence of both widening and longitudinal displacement of the symphysis was found to be in direct proportion to parity. Widening was largest before delivery, decreased after delivery, and had almost disappeared 2 years after childbirth. Longitudinal displacement was found to be unchanged 2 years after delivery, in both primiparae and multiparae. The extent of longitudinal and horizontal displacement depended on age and parity rather than on the baby's weight and the duration of delivery.

N. Alders

348. **Intravenous Progesterone: Basic Effect in Rabbits.**

By W. J. RAPPOPORT, B. GOLDSTEIN and A. L. HASKINS. *Obstet. Gynec.*, **9**, 497–504. May 1957. 1 table. 5 figs. 8 refs.

The authors believe that the large quantity of progesterone elaborated by the placenta during pregnancy is utilized at the site of secretion, prior to its escape into the general circulation. Once in the general circulation it is rapidly deactivated by the liver. The ineffectiveness of progesterone therapeutically in pregnancy may be the result of the quantitative failure of the hormone to reach the uterus before its deactivation. This trouble might be overcome by the intravenous injection of the progesterone, but one difficulty is the finding of a suitable solvent. The authors tried propylene glycol, and in this study they report their results using rabbits as experimental animals.

Toxicity of intravenous propylene glycol and intravenous progesterone in propylene glycol was determined. The maximum plasma level obtained in surviving rabbits was 35 mg. of progesterone per ml. of plasma. Progesterone clearance studies indicated that plasma was cleared of the steroid 30 minutes after injection.

These studies indicate that both propylene glycol and progesterone possess toxicity of considerable significance.

J. G. Dumoulin

349. **Relationship between Nausea and/or Vomiting in Early Pregnancy and Abortion.**

By J. H. MEDALIE. *Lancet*, **2**, 117–119. July 20, 1957. 2 tables. 13 refs.

A hundred consecutive pregnant women were studied to ascertain whether the severity and duration of nausea and/or vomiting in the first trimester is related to abortion. A statistically significant inverse relationship was found between nausea/vomiting and abortions in early pregnancy. No such significance was found between the women's age, parity or period in the country and either nausea/vomiting or abortion. The author concludes that the relationship between nausea/vomiting and abortion suggests some common factor in their aetiology.

H. H. Fouracre Barns

350. **The Physiology of Edema in Pregnancy.**

By E. W. PAGE. *West. J. Surg. Obstet. Gynec.*, **65**, 166–174. May–June 1957.

Oedema is defined as expansion of the interstitial space with isotonic fluid, the movement of this fluid being governed by such factors as capillary pressure, tissue pressure and the colloid osmotic pressures of the plasma and the interstitial fluids. The localized oedema of the legs, so common in the pregnant patient, is due to raised pressure in the veins of the legs caused by mechanical obstruction of the venous return by the gravid uterus when the woman is upright or in the supine position; its treatment is therefore mechanical rather than biochemical. Generalized oedema, on the other hand, is caused by renal glomerulotubular imbalance resulting in the retention of water and sodium, the osmotic pressure of the extracellular fluid remaining constant except when disturbed by severe disease or the physician. The constancy of the osmotic pressure is governed by two mechanisms; osmoreceptors control the secretion of anti-diuretic hormone (ADH) by the pituitary gland while volume receptors (probably in the vascular system of the thorax) control the secretion of aldosterone by the adrenal cortex. These two hormones "advise" the renal tubule how much water and sodium to resorb. Normal pregnancy changes every known factor in the control of body water except osmosis, and it is probable that the placenta secretes sodium-retaining steroids which assist the tubules in resorbing the increased quantities of sodium in the glomerular filtrate. The glomerular filtration rate is raised through most of pregnancy and falls to non-gravid levels in the last month or two; if there is not a corresponding fall in the concentration of the sodium-retaining steroids generalized oedema will result.

The plasma albumin concentration in pregnancy is not reduced by haemodilution but is "set" at a lower level; this may cause a more rapid fluid exchange between capillaries and interstitial space but will not cause oedema. Pregnancy is also marked by the appearance of an enzyme which rapidly inactivates ADH, its source being unknown; imbalance between increased production and destruction may lead to gains or losses of water resulting in the variations in thirst that characterize pregnancy.

Generalized oedema in normal pregnancy results in only minor variations in the glomerular filtration rate, but pre-eclampsia is marked by a pronounced fall in this rate with a persistence or further elevation of the hormonal influences favouring sodium and water re-absorption. The hormonal influences appear to predominate and the result is generalized oedema. The ideal treatment for pre-eclampsia would be elevation of the glomerular filtration rate but since a method of doing this is unknown, the problem is usually solved by extirpating the endocrine organ, the placenta, which presumably caused the glomerulo-tubular imbalance in the first place.

[This is an excellent review of this difficult subject.]

D. C. A. Bevis

351. **Hypotensive Drugs in Pregnancy Toxemia.**

By W. B. CHERNY, F. B. CARTER, W. L. THOMAS and C. H. PEETE, JR. *Obstet. Gynec.*, **9**, 505–511. May 1957. 6 tables. 39 refs.

Most of the drugs used in the management of hypertension and peripheral arterial disease have been tried in pregnancy toxaemia. Only a few have proved valuable.

Magnesium sulphate may be given intravenously as a drip infusion in a dosage up to 30 g. a day or intramuscularly in 5 g. doses. It acts as a peripheral vasodilator, a central nervous system depressant and possibly as a diuretic. But it should not be used when there is marked renal impairment with persistent oliguria.

Veratrum preparations cause a general peripheral vasodilatation without appreciably altering the cardiac output. They also reduce cerebral vascular resistance. Oliguria may occur but is transient. They are useful in toxaemia but sensitivity seems to diminish rapidly with continued use.

Apresoline is a powerful vasodepressor which also causes an increased cerebral blood flow and a rise in cardiac output with tachycardia. It is most effective in acute toxaemia. Toxic reactions, such as headache and palpitations, can be disconcerting. Tolerance to the drug develops rapidly, but can be delayed to some extent if combined with veratrum compounds such as Unitensin.

This combination was used by the authors in 74 cases. Apresoline injections, 10–15 mg., were alternated with Unitensin, 0·2–0·4 ml., at 1–2 hourly intervals. Cases of pre-eclampsia and eclampsia responded better than those with toxaemia superimposed on pre-existing hypertension. There were 11 stillbirths in the series.

Derivates of Rauwolfia serpentina gave unpredictable results and were not satisfactory.

J. G. Dumoulin

352. **Reserpine in Toxemia of Pregnancy.**

By R. LANDESMAN, W. D. MCLARN, R. N. OLLSTEIN and B. MENDELSOHN. *Obstet. Gynec.*, **9**, 377–383. Apr. 1957. 3 tables. 2 figs. 11 refs.

Much evidence suggests that there is widespread vasoconstriction in toxaemia of pregnancy. Varied drugs have been used in an effort to improve blood flow to the uterine-placental area. The authors report on the use of Reserpine in 80 pregnant patients with chronic hypertension and 28 with acute pre-eclamptic toxaemia at the New York Lying-In Hospital. The drug was given by mouth or intravenously without significant toxicity to mother or foetus.

No improvement in foetal salvage or incidence of small babies was found with prolonged oral reserpine therapy. The treatment appears to delay the superimposition of pre-eclampsia. It masks the manifestations of superimposition while in no way modifying the basic toxaemia process.

A review of anti-hypertensive agents reveals that none alters the foetal outcome in toxaemia. Maternal protection may be afforded with these preparations by preventing hypertensive crises.

J. G. Dumoulin

353. **Protein in the Urine During Pregnancy: A Simple Quantitative Method of Estimation.**

By M. P. WEARING. *Obstet. Gynec.*, **9**, 549–553. May 1957. 3 figs. 8 refs.

The method of Kingsbury *et al.* (*J. Lab. clin. Med.*, 1926, **11**, 981) for determining the amount of protein in the urine was compared by the author with the very accurate Kjeldahl method. There was a very satisfactory correlation for amounts of protein from 0 to 100 mg. per 100 c.c.

The method which proved accurate and rapid was as follows: 2·5 ml. of urine were added to 7·5 ml. of 3 per cent sulphosalicylic acid and well mixed. After standing for 10 minutes, the solution was compared with standards. The method of making the standards is described.

The normal amount of protein in the urine of antenatal patients is 0 to 15 mg. per 100 ml. The amount increases from the first to the third trimester. More than 15 mg. indicates an early toxaemia.

J. G. Dumoulin

354. **Electrocardiography in Pregnancy.** (L'elettrocardiografia in gravidanza.)

By G. GARBAGNI. *Minerva ginec., Torino*, **9**, 181–192. Mar. 31, 1957. 6 figs. 42 refs.

The problem of pregnancy complicated by heart disease has undergone re-valuation in recent years due to electrocardiographic studies and advances in cardiac surgery. Especially in the last three months pregnancy produces characteristic changes in the axes of electrocardiac activity due to the uterine enlargement pushing up the diaphragm. In spite of increased effort being required of the left ventricle the latter rarely shows any hypertrophy. These displacements of the heart explain the flattening or inversion of the P wave and other changes in the electrocardiograph. In labour, in normal subjects, the only additional changes are increased frequency of heart beat, and in neurolabile subjects some extra systoles. These signs are reversible if organic heart disease is not present, and in the puerperium the E.C.G. returns to normal.

In toxaemic cases the E.C.G. shows signs of myocardial strain and ischaemia due to overloading of the left ventricle, and if organic heart disease is also present these warning signs are even more marked. After delivery abnormalities in the tracing tend to disappear concurrently with the improvement in the clinical picture.

In organic heart disease uncomplicated by toxaemia the pregnancy does not materially alter the characteristic E.C.G. of the particular heart affection.

W. C. Spackman

355. **Four Cases of Megaloblastic Anaemia of Pregnancy and the Puerperium.**

By I. M. PATZ. *S. Afr. med. J.*, **31**, 384–386. Apr. 20, 1957. 14 refs.

The author describes 4 cases of megaloblastic anaemia of pregnancy and the puerperium seen in African women in a 2-year period at the Middelburg Hospital. The comparative rarity of the condition is discussed. In all cases the diagnosis was originally missed on account of the varied modes of presentation. The first patient presented with diarrhoea, weakness and lassitude after delivery. She was pyrexial, and did not respond to antibiotics and intravenous iron. Diagnosis was made on sternal puncture.

The second patient complained of breathlessness on exertion, and a harsh systolic murmur was heard at the apex. Four weeks after delivery she was re-admitted with mild cardiac failure and severe anaemia. Megaloblasts were found in the peripheral blood.

The third patient presented with the clinical picture of deep vein thrombosis, progressive in spite of anticoagulant therapy.

The fourth patient was admitted in a semi-comatose state 1 week after a 6 months' abortion. She was pyrexial, pale and had tachycardia and abdominal tenderness. She was transfused and given antibiotics. Her condition deteriorated until vitamin B_{12} was administered in 100 microgram doses. Improvement was then rapid.

The diagnosis was confirmed by bone marrow examination in all cases. The difficulties of clinical diagnosis with these varied modes of presentation are discussed. There may be an associated iron-deficiency.

In South Africa response to treatment is variable, and either vitamin B_{12} or folic acid may be effective, with folic acid probably the drug of choice.

L. J. Abramowitz

356. **Placental Transmission of the L.E. Factor.**

By G. M. BERLYNE, I. A. SHORT and C. F. H. VICKERS. *Lancet*, **2**, 15–16. July 6, 1957. 9 refs.

The authors report 2 cases of systemic lupus-erythematosus in pregnancy. In approximately 90 per cent of cases of systemic lupus-erythematosus (S.L.E.) large numbers of lupus-erythematosus cells (L.E. cells) are demonstrable in preparations of peripheral blood

or bone-marrow. In the 2 cases reported the diagnosis of S.L.E. in the mothers was made on strong clinical grounds. L.E. cells were found in the blood of each infant up to the 7th week although there was no evidence of ill health in either child.

H H. Fouracre Barns

357. **The Effects of Radioactive Iodine on Maternal and Fetal Thyroid Function During Pregnancy.**

By K. P. RUSSELL, H. ROSE and P. STARR. *Surg. Gynec. Obstet.*, **104**, 560–564. May 1957. 4 tables. 2 figs. 7 refs.

The use of radioactive iodine as a diagnostic or therapeutic agent during pregnancy is considered to be contra-indicated because the foetus may suffer damage to the thyroid gland with resultant hypothyroidism. Such damage is particularly liable to occur because of the extraordinary avidity which foetal thyroid tissue possesses for the isotope.

Two cases are described in which radioactive iodine was administered at about the 13th week of pregnancy for the treatment of recurrent thyroid carcinoma. Both infants suffered from congenital hypothyroidism and in both subnormal levels of protein-bound iodine were found. One infant died at the age of 11 weeks of a respiratory infection and at autopsy no demonstrable thyroid tissue was found. The second child was alive at the age of five months and was receiving a maintenance dose of 1½ grains of thyroid extract daily.

The authors consider that in the early detection of congenital hypothyroidism the determination of protein-bound iodine in the cord blood may prove of value.

John P. Erskine

358. **Perinatal Mortality in the Unsuspected Diabetic.**

By P. PEDOWITZ and E. L. SHLEVIN. *Obstet. Gynec.*, **9**, 524–532. May 1957. 1 table. 1 fig. 27 refs.

The authors have selected cases from the 301 viable diabetic pregnancies delivered at the Jewish Hospital of Brooklyn between 1932 and 1956 to point out various conclusions they have reached.

They believe that an abnormal glucose tolerance test during pregnancy represents diabetes in its earliest stages. The hyperglycaemia may be temporary and revert to normal when the pregnancy terminates, but diabetes will manifest itself sooner or later in these cases. Pregnancy is a sensitive barometer of the functional ability of the islands of Langerhans and may reveal that diabetes exists before it is clinically recognizable.

Isolated fasting blood sugar determinations may fail to reveal diabetes. Post-prandial rather than fasting urine specimens should be tested, for thereby a greater number of unsuspected diabetics will be found.

A large premature infant should not invariably be attributed to miscalculation. While large babies are the rule in diabetic pregnancies, small infants do not rule out diabetes. The diabetic mother's newborn baby has features resembling those of Cushing's disease; the face is plethoric and oedematous. At post-mortem cardiac hypertrophy, hyperplasia and hypertrophy in the islets of Langerhans, excessive erythropoietic centres in the liver, and the presence of numerous nucleated red cells in the peripheral blood help in the recognition of the condition.

The foetal loss in 160 viable diabetic pregnancies since 1950 was 8·8 per cent.

J. G. Dumoulin

359. **Cervical Cancer in Pregnancy: Review of the Literature with Presentation of Thirty Additional Cases.**

By R. W. KISTNER, A. C. GORBACH and G. V. SMITH. *Obstet. Gynec.*, **9**, 554–560. May 1957. 7 tables. 26 refs.

This is a statistical review of 106 cases of cervical cancer in pregnancy from the world literature in which the duration of pregnancy, stage of disease, and 5-year results were available. Patients treated during the 4 months post-partum are included. In addition, 20 new cases are reported by the authors from the Free Hospital for Women, and 10 new cases from the Massachusetts General and Pondville State Hospitals in Massachusetts.

Cancer of the cervix is said to occur once in every 2,000 pregnancies. Pregnancy complicates about 1 per cent of all cervical cancers. The majority of cases occur in the 31 to 35 age group and are multiparous (average parity 4·9).

Vaginal bleeding occurred in 77 per cent, there were no symptoms in 14 per cent, and in 9 per cent the diagnosis was made during labour because of abnormal bleeding or failure to progress. The majority of cases were of squamous-cell type but the histological type does not affect the radio-sensitivity or 5-year survival rate. Survival is dependent upon the stage of the disease.

Therapy consists of radiation, surgery and combinations of both, and depends on the particular trimester in which diagnosis is made. During the first two trimesters radium and X-rays, or radium and radical hysterectomy, may be employed, depending on the stage. During the last trimester classical Caesarean section should be performed followed by radium or radical hysterectomy.

Analysis of results indicates that, prior to the middle of the last trimester, the 5-year survival rate does not appreciably differ from that of the non-pregnant state when compared stage for stage. The apparent cure rates in the last half of the third trimester and during the post-partum state are poor.

J. G. Dumoulin

360. **Jaundice in Pregnancy: A Review from the Charity Hospital, New Orleans, 1941–1956.**

By C. R. VINCENT. *Obstet. Gynec.*, **9**, 595–598. May 1957. 1 table. 12 refs.

Thirty-two cases of jaundice in pregnancy are reviewed, an incidence of 0·02 per cent. Twenty-five were in negroes. Hepatitis was the leading cause accounting for 23 cases. In this group, there were 6 maternal deaths and 6 foetal deaths. Five of the foetal deaths were spontaneous abortions, all occurring before the 28th week. When hepatitis occurs in the last trimester, there is a much higher maternal and foetal survival rate.

Other causes of jaundice included homologous serum jaundice, Weil's disease, hepatic poisons, adenocarcinoma of the common bile duct, obstruction of the bile duct, and sepsis.

J. G. Dumoulin

361. **Interstitial Pregnancy Following Homolateral Salpingectomy: Report of Three Cases.**

By D. T. CONLEY and J. A. KLIEGER. *Obstet. Gynec.*, **9**, 605–607. May 1957. 17 refs.

Three cases of pregnancy are described occurring in the interstitial portion of the Fallopian tube after previous salpingectomy on that side. This brings the total number of cases reported to 38.

The mechanism of occurrence of this type of ectopic pregnancy is obscure but it may be due to regeneration of the patency of the previously excised tube. The frequency of this complication does not justify routine wedge resection of the interstitial portion of the tube at the time of salpingectomy as this may be an extensive procedure and it may leave a uterus which will rupture if a subsequent pregnancy occurs.

In one case of the authors, wedge resection was carried out; in the other two subtotal hysterectomy was performed.

J. G. Dumoulin

LABOUR

362. **Oxytocin: Action and Current Usage.**

By R. G. DOUGLAS and R. W. BONSNES. *West. J. Surg. Obstet. Gynec.*, **65**, 89–94. Mar.–Apr. 1957. 18 refs.

Much work has been done on the chemistry and pharmacology of oxytocin during the past few years. The hormone has been isolated in its pure form, its structure determined and it has been synthesized. It is closely related to vasopressin and both substances are polypeptides composed of amino-acids combined in peptide linkage. A recent development in its use is the continuous intravenous infusion to induce or stimulate labour, and this is most effective if the dosage is kept small in the initial stages and then steadily increased, this being the probable mechanism in natural labour. Providing there are no undesirable side effects for mother or baby the total amount of pitocin used in such an infusion is immaterial; the obstetrician must however be in attendance to assess the effect on the patient and her baby. The authors induce labour with 4 units of pitocin in 500 ml. of glucose solution (they point out that 1 unit is equal to 2 micrograms of the pure substance), running in this solution very slowly at first to judge its effects and then increasing the rate as required. If there is little response they increase the concentration and have used as much as 80 units to 500 ml. without untoward results. In experienced hands the only contra-indication is definite cephalopelvic disproportion, but they stress that care must be used at all times. The use of the continuous infusion is also of value during Caesarean section and for the prophylactic therapy of post-partum haemorrhage. Oxytocin has an effect on the breasts and it may be used to relieve breast engorgement in the mother who wants to feed her child but seems unable to do so; it is of little use for the engorgement due to venous or lymphatic stasis as occurs on the second to fourth day post-partum. In the normal lactating woman on the fourth to eighth day, 0·5 unit of pitocin intravenously produces milk ejection within 20–30 seconds, intramuscular injection takes 1–2 minutes to be effective. This use of oxytocin is still in its infancy but appears to be very promising and the authors consider that further work along these lines is likely to be rewarding.

D. C. A. Bevis

363. **Use of Synthetic Oxytocin for Medical Induction of Labour.** (Zur Verwendung eines synthetischen Oxitozin in der medikamentösen Geburtsleitung.)

By L. VELIKAY. *Zbl. Gynäk.*, **79**, 846–853. 1957. 2 tables. 48 refs.

The author reports on a series of patients admitted to the Second Gynaecological Clinic of the University of Vienna. Synthetic oxytocin ("syntocinon") has been proved to have actions quantitatively and qualitatively identical with those of natural purified oxytocin. Its advantages over the natural product are the absence of vasopressin impurities and therefore avoidance of antidiuretic and pressor effects.

Syntocinon was used for induction of labour and gave best results by continuous intravenous infusion (1 unit per 100 ml. of 5 per cent glucose solution). Amongst 32 patients this method failed in 3. In one of these tonic contraction of the uterus in a primigravida of 38 with undiagnosed twins was treated by Caesarean section.

The author gives the following indications for the infusion method of medical induction:

(1) Failure of onset of labour within 24 hours following premature rupture of the membranes at term;
(2) Postmaturity;
(3) Intra-uterine death;
(4) Non-viable malformations;
(5) Febrile illness of the mother endangering the life of a viable foetus;
(6) All remaining indications for induction of labour in which other methods were contra-indicated.

Contra-indications to the continuous infusion method are all forms of disproportion; conditions in which the uterus is over-distended, particularly twin-pregnancy (in one case of twin-pregnancy continuous infusion was followed by the deaths of both foetuses); uterine scars; advanced diseases of the heart and circulation.

Intermittent intramuscular injections of $\frac{1}{2}$ to 2 units of syntocinon were given to 126 cases of inertia with very good results. In 3 cases of inertia, the author used the drip method.

A single intravenous injection of 3 to 5 units of syntocinon was given in 15 cases of breech labour when manual assistance was required, and in 4 forceps deliveries.

The preparation was thus found to be as effective as natural oxytocin for medical induction and for inertia.

Syntocinon was also given a trial in 20 patients for the prevention of atony following delivery; for the treatment of atony in 2 and for the effective control of mild post-partum haemorrhage in 8 patients. Nevertheless the author expresses his preference for ergot preparations for routine use after delivery.

Bruce Eton

364. **Induction of Labour by Perfusion of Hypertonic Saline Solution into the Lower Uterine Segment (Aburel-Elias Method).** (Declansarea travaliului prin perfuzii tocogene intersegmento-ovulare (Procedeul Aburel-Elias.)

By E. Aburel, A. Mirescu and P. Elias. *Obstet. Ginec.* (*Bucarest*), 283–289. Sept. 1956. 3 figs. 7 refs.

The authors describe a method for the interruption of pregnancy during the last trimester and claim to have been successful in each of the 31 cases of labour they have induced in this manner. Their method is claimed to act by stimulating the baro- and chemical receptors in a restricted area of the lower uterine segment. The membranes are separated widely round the internal orifice and the lower segment without rupturing them. A coiled rubber catheter 5–6 cm. in diameter is introduced into the prepared area and 300 ml. of a 20 per cent sodium chloride solution containing penicillin is injected through the catheter at the rate of 50 drops a minute, the catheter being left *in situ* until the cervix is approximately 4–5 cm. dilated. If contractions have not started within two to three hours, more of this solution can be injected into the lower segment. Prior to the perfusion the authors give the patient 30 mg. of folliculin, and in some cases of hypotonic inertia they advocate intravenous oxytocin.

The cases were induced for postmaturity, cardiac or pulmonary disease of the mother, and also for Rh and ABO incompatibility. The average interval between induction and labour was twenty hours. There were no ill effects to mother or baby. *Sylvia Lerer*

365. **Dihydroergotamine in the Treatment of Spasticity in Labour.** (Contributo clinico-sperimentale sull'azione spasmolitica cervicale della diidroergotamina nel travaglio di parto.)

By G. Tallo and D. Roccapalumba. *Minerva ginec., Torino*, **9**, 27–32. Jan. 15, 1957. 4 figs. 2 tables. 10 refs.

This article deals with the effects of administering dihydroergotamine to 121 women (46 primiparae and 75 multiparae) in whom there was marked delay in labour due to functional failure in dilatation of the cervix. Hysterotonographic tracings of uterine contractions were made and these bear out the clinical impression that the uterine action becomes both more regular and more forceful after the administration of 0·2 mg. of this drug, and that as a result labour is completed without abnormal delay thereafter.

Six primiparae out of 46 required forceps, and 4 out of 75 multiparae, the remainder were all delivered spontaneously. Moreover, so far from there being any evidence of ill effect on the foetus, any cardiac arrhythmia observed at the stage of failure of cervical dilatation was replaced by normal and regular foetal heart beat as soon as the drug had had time to take effect. *W. C. Spackman*

366. **Labour Shortened by Intradermal Infiltration.** (Studiul scurtarei duratei travalilui prin infiltratii intradermice.)

By N. N. Gherghiu, Z. Rozenthall, C. Gabreanu, O. Rodan, J. Savescu, S. Saler, M. Barbu and I. Roman. *Obstet. Ginec.* (*Bucarest*), 209–220. July 1956. 7 figs. 28 refs.

The authors have studied this method of shortening the duration of labour in 552 cases, both in primigravidae and multiparae, by injecting 10 ml. of a 3 per cent procaine solution and 1 ml. of a 1 per cent atropine solution in the suprapubic and sacro-iliac regions. It is claimed that labour is shortened because of relaxation of the cervix and the pelvic floor muscles, and more regular uterine action. There is only a moderate analgesic effect but the method is effective for cervical dystocia and for uterine dysfunction. It has a special application in cases of premature rupture of membranes.

The method is devoid of ill effects to mother and foetus and can be repeated two to three times during labour. It is a good adjuvant in psycho-prophylaxis for pain during childbirth. The authors compare this method with other procaine infiltrations and claim that it is more efficient and, at the same time, reduces obstetrical interventions. *Sylvia Lerer*

367. **Double Pregnancy. Report of a Case with Thirty-five Days Between Deliveries.**

By R. H. Abrams. *Obstet. Gynec.*, **9**, 435–438. Apr. 1957. 1 table. 2 figs. 7 refs.

The author reports a double-ovum twin pregnancy, with a 35-day interval between the births of the first and second twins. The first was born at home, a living female infant weighing 14 ounces, which died 3 hours later. The placenta was retained *in utero*. The cord was clamped and divided close to the cervix. The second twin, born 35 days later, weighed 2 pounds 4½ ounces and appeared vigorous. Its placenta was delivered spontaneously. The still-attached placenta of the first twin was then manually removed. Lactation did not commence until 3 days after delivery of the second twin. At 12 weeks post-partum a hysterosalpingogram revealed a normal uterus. *J. G. Dumoulin*

368. **A Case of Conjoined Twins.**

By T. W. Roddie. *Brit. med. J.*, **1**, 1163–1164. May 18, 1957. 1 fig. 5 refs.

The author, from the University of Malaya, Singapore, describes a case of conjoined twins occurring in a Cantonese woman admitted to the Kandang Kerbau Hospital. She was aged 30, and at the thirty-second week of her eighth pregnancy. All seven previous confinements had been normal. The blood pressure was 160/100 mm. Hg, and there was albuminuria and oedema. An X-ray film of the abdomen revealed twins presenting by the breech, with the heads at the same level and facing each other.

She was anaesthetized at full dilatation, and with traction all four feet were drawn down and the bodies delivered. The legs were drawn forward to allow the posterior head to be born first, followed easily by the anterior head. A single placenta with velamentous insertion of the cords at opposite sides was delivered. The foetuses were fresh, and one made feeble efforts to breathe.

The combined weight of the twins was 4 pounds 10 ounces. They were joined by a bridge of skin-covered soft tissue just below the xiphoid processes. Both infants showed exomphalos, and there appeared to be a large common liver.

Eileen Wilson

369. **Spontaneous Intra-uterine Rupture of the Umbilical Cord. Report of a Case.**

By J. J. FOLDES. *Obstet. Gynec.*, **9**, 608–609. May 1957. 6 refs.

In the case reported, spontaneous intra-uterine rupture of a normal umbilical cord occurred at the end of the first stage of labour. The cord was coiled around the neck of the infant, thus becoming relatively short. The rupture probably occurred when the head descended, thus tightening the cord. The infant was stillborn.

J. G. Dumoulin

370. **A Simple Procedure for the Treatment of Cord Prolapse.** (Ein einfaches Verfahren zur Behandlung des Nabelschnurvorfalls.)

By L. ZELENKA. *Zbl. Gynäk.*, **79**, 937–938. 1957.

The author makes a preliminary report from the Gynaecological Department of the University of Szeged (Hungary). He suggests the introduction of a thick-walled rubber tube, 25–30 cm. long and 2·5 cm. wide. The tube is placed between the cervix and the head near the loop of cord in order to prevent pressure of the head on the cord. This would allow time for reposition of the cord or Caesarean section. The manœuvre had recently been used successfully in two cases.

Bruce Eton

371. **Placenta Accreta in Cesarean Scar: Report of a Case.**

By A. SEDLIS, J. W. FINN and C. H. LOUGHRAN. *Obstet. Gynec.*, **9**, 575–579. May 1957. 1 table. 2 figs. 17 refs.

Placenta Accreta: Review of the Literature and Report of Four Cases.

By W. N. ROTTON and E. A. FRIEDMAN. *Obstet. Gynec.*, **9**, 580–585. May 1957. 1 table. 1 fig. 50 refs.

In the first of these two contributions on placenta accreta, a case is described in which a repeat Caesarean section was performed on a patient. Half the placenta was firmly adherent to the thin lower segment, so that subtotal hysterectomy was necessary to control the haemorrhage. The Caesarean scar was thought to be the cause of the placenta accreta. In over 200 cases of placenta accreta reported there were 17 where a Caesarean scar was the possible aetiological factor.

The authors of the second paper have found 240 cases in the literature to which they add details of 4 more occurring during the last 24 years at the Sloane Hospital for Women, New York. Because of the dangers of haemorrhage, rupture of the uterus (spontaneous or traumatic), inversion of the uterus, and sepsis, removal of the placenta should not be attempted. Hysterectomy is much safer.

J. G. Dumoulin

372. **True Sacculation of the Pregnant Uterus.**

By D. A. DALLAS. *West. J. Surg. Obstet. Gynec.*, **65**, 130–134. May-June 1957. 1 fig. 5 refs.

The author, from Stanford University, reviews the literature and adds 2 cases to the 12 already reported. The first patient, a primigravida aged 24, had a normal antenatal period and normal delivery at 36 weeks. The placenta could not be expressed and after an attempt at manual removal had failed to locate it, the abdomen was opened. A thin-walled sac the size of a grapefruit was found at the fundus of the uterus just medial to the left round ligament. This sac was opened and the contained placenta removed, the sac immediately began to retract and the incision was closed with catgut sutures. Two years later the patient became pregnant again; Caesarean section was performed at term and the only evidence of the defect was a depressed linear scar.

The second patient was aged 29, had had one child and 2 abortions and had been curetted twice. After a normal pregnancy and delivery the placenta could not be expressed and uterine exploration showed it to be in a pouch on the right side of the fundus. Manual removal was successful and post-partum examination did not reveal any abnormality. The aetiology of the condition is unknown and diagnosis difficult, in neither case was bimanual examination helpful. Treatment consists of emptying the sac, the condition rights itself and subsequent pregnancy may be permitted without fear of recurrence or uterine rupture. *D. C. A. Bevis*

373. **The Management of Post-partum Pain with Dihydrohydroxycodeinone (Percodan). Evaluation with Codecine and Placebo.**

By J. J. BONICA, D. HADFIELD and B. BENNETT. *West. J. Surg. Obstet. Gynec.*, **65**, 84–88. Mar.-Apr. 1957. 12 refs.

Dihydrohydroxycodeinone is claimed to have analgesic properties between those of morphia and codeine, it is relatively non-toxic and its properties are enhanced by combination with aspirin, phenacetin and caffeine. A study was carried out at the University of Washington on 143 patients complaining of pain after delivery. These patients were given tablets containing one of the following: (*a*) codeine 21·6 mg. with equal amounts of aspirin, acetophenetidin and caffeine, (*b*) an inert placebo or (*c*) "Percodan" containing dihydrohydroxycodeinone hydrochloride 4·5 mg., dihydrohydroxycodeinone terephthalate 0·38 mg., aspirin 224 mg., acetophenetidin 160 mg., caffeine 32 mg. and homatropine terephthalate 0·38 mg. The relief was graded as excellent when relief was complete for 3 hours or more, and adequate when the effect lasted for at least 2 hours; 90 per cent of patients graded Percodan in these groups compared with 70 per cent for codeine. Side reactions such as nausea and vomiting were the same for both Percodan and codeine. The authors conclude that the drug is worthy of further clinical trial.

D. C. A. Bevis

374. **Trends in Obstetrical Anesthesia Following Acceptance of Twenty-Four-Hour Physician Anesthesia Service.**

By C. LINDSTROM and D. C. MOORE. *West. J. Surg. Obstet. Gynec.*, **65**, 63–68. Mar.–Apr. 1957. 5 refs.

In October, 1952 the Mason Hospital, Seattle, introduced a service whereby physician-anaesthetists were continuously on call for the Obstetric Department. Since then the number of regional block procedures (particularly continuous caudal anaesthesia) have increased while the number of general anaesthetics has declined. This has resulted in greater safety for the patient and the cost has not proved excessive.

D. C. A. Bevis

LACTATION

375. **The Treatment of Puerperal Mastitis with Rovamycin.** (Ueber die Behandlung der Mastitis Puerperalis mit Rovamycin.)

By W. NEUWEILER and P. RITTER. *Geburtshilfe und Frauenheilkunde*, **17**, 405–413. May 1957. 4 tables. 4 figs. 6 refs.

A report from the University Frauenklinik, Bern, deals with 50 cases of puerperal mastitis treated with Rovamycin ("Specia" brand spiramycin), in doses of 5 g. daily for two days, 4 g. daily for two days and 3 g. on the fifth and sixth days. If there was abscess formation the pus was aspirated and 500,000 units of penicillin were injected into the abscess cavity. In all cases this treatment was supplemented by expressing the breasts and either applying infra-red or short-wave diathermy. Incision of the breast was never necessary. All the cases responded promptly and completely with this regime.

The authors found an increase from 0 per cent up to 8 to 10 per cent in the resistant strains of Staphylococci to Rovamycin, during the early months of the investigation.

The Rovamycin was given by mouth in divided doses at six-hourly intervals. It was better tolerated than other oral antibiotics and no serious toxic effects were noted.

A bacteriostatic method of estimating the amount of active Rovamycin excreted in milk, is described. Excretion curves of Rovamycin in human milk, using different doses of the drug, were obtained and are published.

Peter J. Huntingford

INFANT

376. **A Possible Method of Foetal Sex Determination.**

By A. M. STEWART and J. MCKENZIE. *Brit. med. J.*, **1**, 1396–1398. June 15, 1957. 9 refs.

The authors (from Aberdeen) noticed an unusual form of foetal vertebral body ossification during the course of routine obstetric radiography. It consisted in a ventral and a dorsal centre of ossification, with an intervening oval or linear translucency. It was commonly observed in the lumbar region. This coronal cleft is only visualized when the foetus is in the true lateral position. The antero-posterior diameter of the ossified centrum of the affected vertebra is increased, probably due to a posterior extension at the expense of the synchondrosis.

The authors found that if this defect is present in a foetus over 28 weeks maturity there is a 93 per cent probability that the foetus is male. By 35 weeks maturity the probability has risen to 98 per cent. Before the 28th week the normal proportion of ventral and dorsal ossification centres shows no male bias.

Eileen Wilson

377. **Observations Regarding Prenatal Sex Determination in Maternal Blood Films.** (Bemerkungen zur pränatalen Geschlechtsbestimmung aus dem Blutbild.)

By E. BERGEMANN. *Zbl. Gynäk.*, **79**, 689–696. 1957. 2 tables. 38 refs.

In a proportion of segmented neutrophile leucocytes small nuclear appendages are observed which make it possible to determine the sex of the individual.

The author studied blood films of 214 pregnant women shortly before delivery in order to establish whether the sex of the foetus had any influence on the morphological appearance of these nuclei. He found that male foetuses did not cause any structural change in the maternal leucocytes.

These findings were not unexpected. The maternal leucocyte carries the somatic chromatin of the individual. There is no evidence that it can be changed fundamentally by hormonal influence. Nuclear characteristics depending on the sex of the foetus can therefore only be found in foetal cells.

Bruce Eton

378. **The Transfer of Blood Between Baby and Placenta in the Minutes after Birth.**

By M. GUNTER. *Lancet*, **1**, 1277–1280. June 22, 1957. 7 figs. 17 refs.

The author has studied the transfer of blood between the placenta and the baby by continuous records of the baby's weight after vaginal delivery and after Caesarean section. If the cord is left untied a baby will usually increase his blood volume by a significant amount which is roughly correlated to the baby's weight. Large losses were also observed and were attributed to loss through patent umbilical arteries and by siphonage when the baby was held higher than the placenta.

H. H. Fouracre Barns

379. **Morphological Studies of the Ovaries of Newborn Children and Infants with Special Reference to the Pre-Natal History.** (Morphologische Untersuchungen an Neugeborenen- und Kleinkinder-Ovarien unter besonderer Berücksichtigung der "pränatalen" Anamnese.)

By H. H. STANGE and M. DITTMANN. *Zbl. Gynäk.*, **79**, 729–745. 1957. 1 table. 17 figs. 31 refs.

The authors examined 50 ovaries of 27 children. Four of these were stillborn, 9 died within 24 hours, 9 within 10 days of birth and 5 within the first 7 months of life.

They found that during the second half of pregnancy extensive formation of primordial follicles occurs in the foetal ovary. During the eighth and ninth months growth and atresia of follicles occurs. A corpus fibrosum was observed as early as the 38th week of pregnancy.

Differentiation of the cells of the theca interna also begins during the eighth month. A true corpus luteum, however, does not develop.

In infants of toxaemic mothers considerable changes were observed: cystic or fibrous atresia of the Graafian follicles, marked vascular congestion, and hyperplasia and luteinization of numerous interstitial and theca interna cells. These changes are attributed to a high titre of chorionic gonadotrophin (F.S.H. and L.H.) acting on the foetal ovaries. The authors point out the resemblance between the appearances of the foetal ovaries in toxaemic pregnancy and those of the Stein-Leventhal syndrome described in mature women. In both conditions there is a reduction in primordial follicles, the tunica albuginea is thick and there are numerous atresic follicles surrounded by a hyperplastic theca interna.

The authors suggest the possibility that the Stein-Leventhal syndrome may derive from the foetal condition described.

[Human chorionic gonadotrophin is mainly luteinizing. It probably does not possess any F.S.H. action.]

Bruce Eton

380. **Mongolism and Other Congenital Abnormalities.** By M. J. PLEYDELL. *Lancet*, **1**, 1314–1319. June 29, 1957. 8 figs. 14 refs.

The author has ascertained the distribution and incidence of mongols and congenitally abnormal babies born during the twelve years from 1944 to 1955 in Northamptonshire. In many cases the births were aggregated in certain districts of the county. The geographical distribution of the births of mongols and babies with congenital heart disease suggested to the author a common aetiological factor, since on occasions both conditions arose in the same area at about the same time. The importance of establishing the association between infections and congenital abnormalities lies in the possibility of prevention.

H. H. Fouracre Barns

381. **The Role of Exposure of Pregnant Women to Virus Diseases in the Aetiology of Congenital Malformation.** (Role de l'exposition des femmes enceintes aux maladies à virus dans l'étiologie des malformations congénitales.)

By M. DUMONT. *Gynéc. Obstét.*, **56**, 99–105. Jan.–Mar. 1957. 16 refs.

The writer points out that it is difficult to be certain whether a pregnant woman has had a virus infection in the past. Memory is unreliable and retrospective diagnosis is not always precise, particularly for rubella. For this reason the investigation was not easy.

Two criteria were insisted upon in this study:

(1) The exposure to the infection was certain. (2) The mother did not present any suspicious symptoms in the days following the contact.

The cases were then divided into three groups:

(1) Immune women. (2) Non-immune women. (3) Doubtful cases as regards maternal immunity.

One hundred and seventy-eight women exposed in the course of their pregnancy to the following infections were studied: 22 to rubella, 78 to measles, 44 to chickenpox and 34 to mumps. Exposure occurred on 102 occasions in the first trimester, 76 times in the second and third trimesters. Only rubella and measles appeared to affect the foetus.

Fifteen to 21 per cent of the mishaps were in the form of malformations, miscarriages, premature labours or stillbirths. If the malformations only were considered this comprised only 9 per cent in the case of rubella and 8 per cent in the case of measles.

The writer considers the foetus is affected by virus infections through metabolic changes resulting in disturbance of embryogenesis, particularly in gestations which have a special predisposition to this from deficiency of vitamins circulating in the blood.

As regards prophylaxis expectant mothers must avoid contact, particularly in the first three months, and convalescent serum is recommended. Injections should begin in the first three days following contact. The author considers that gamma globulins have a protective action, although Krugman and Ward do not agree.

D. Maxwell

382. **Haemolytic Disease of the Newborn. Deaths in England and Wales During 1953 and 1955.**

By W. WALKER and P. L. MOLLISON. *Lancet*, **1**, 1309–1314. June 29, 1957. 2 figs. 5 tables. 11 refs.

The authors have examined the clinical records of all infants certified as dying from haemolytic disease of the newborn in England and Wales during 1953 and 1955. The numbers of deaths are at least three times as numerous as would be expected with modern treatment. This is due to (1) failure to predict the disease before birth or to diagnose it early enough after birth, and (2) failure to attempt an exchange transfusion or to perform it satisfactorily.

The authors conclude that adequate antenatal investigation with early diagnosis of haemolytic disease of the newborn and early exchange transfusion expertly performed could reduce the present death rate and save more than 150 infants each year.

H. H. Fouracre Barns

383. **Haematogenous Osteitis in the Newborn.**

By J. BOYES, A. E. BREMNER and G. A. NELIGAN. *Lancet*, **1**, 544–548. Mar. 16, 1957. 7 refs.

Forty cases of neonatal osteitis were treated with antibiotics. When possible reliance was placed on the *in vitro* sensitivity of the organism when choosing the antibiotic. Stress is laid on early diagnosis and the institution of the antibiotic treatment for a reasonable length of time. Surgical treatment has been directed to removing pus by aspiration through a short large-bore needle. No immobilization was used in most of the cases.

H. H. Fouracre Barns

384. **The Problem of Intra-uterine Deaths.** (Il problema della morte endouterina del feto.)

By P. N. SILIQUINI and C. A. CAPETTI. *Minerva ginec., Torino*, **9**, 229–260. Apr. 15, 1957. 14 tables. 3 figs. 346 refs.

Evaluation and classification of intra-uterine deaths has many difficult and uncertain factors. This long and detailed article is not only an elaborate theoretical discussion of classification but an analysis of 110 deaths of infants before labour where the foetal weight was not less than 1,000 grammes. Such an analysis aims to show factors which might have been treated before deterioration of the foetus was irreversible, or factors which might recur and require treatment in subsequent pregnancies.

Causes of intra-uterine death may be underlying as well as terminal, and can be maternal, foetal or foeto-maternal. Diagnoses such as asphyxia, congenital debility, prematurity or atelectasis are not of value by themselves for formulating means of reducing such deaths. Asphyxia in particular can be shown to have been present in many cases when the real cause was perhaps gross malformation of the foetus or premature separation of the placenta. Similarly it is not sufficient to discover that immaturity is a frequent concomitant, it is necessary to search for the antenatal conditions most frequently associated with it.

The 110 intra-uterine deaths here examined are analyzed for underlying causes and terminal processes as well as for maternal, foetal or combined causes and compared with statistics published by others. The chief maternal factors were judged to be responsible for the following percentages of deaths: toxaemia 33 per cent, prolonged pregnancy 20, premature separation of the placenta 13·6, diabetes and syphilis 4·5, placenta praevia 3·6 and Rhesus iso-immunization 2·7 per cent. Foetal malformations accounted for 11 per cent and indeterminate factors 7 per cent. Other inferences drawn were that stillbirths of dizygous twins were 3 or 4 times, and monozygous 6 or 7 times more frequent than those of single foetuses. Fifty per cent of twin pregnancies end prematurely. Maternal age and multiparity are positive factors in increasing intra-uterine deaths but sex of the foetus shows no influence.

W. C. Spackman

OBSTETRIC OPERATIONS

385. **Five Years' Experience of Prophylactic External Cephalic Version.** (Fünfjährige Erfahrungen mit der prophylaktischen Wendung auf den Kopf durch äussere Handgriffe bei Beckenendlage.)

By E. LINDNER. *Geburtsh. u. Frauenheilk.*, **17**, 557–566. June 1957. 3 tables. 34 refs.

This is an article from the other side of the iron curtain, in which the author covers ground already well-documented elsewhere. A series of prophylactic external cephalic versions has been carried out in the Frauenklinik of Palacky University, Czechoslovakia.

An historical survey of the subject is presented, as well as a discussion of the aetiology and incidence of breech presentation and a discussion of the indications and contra-indications for external cephalic version. The author describes the method used, and in all respects his views conform with the trends of current British practice.

Version was usually attempted between the 34th and 36th weeks of pregnancy, a few were attempted after this time. The total number of cases in the series was 64. Anaesthesia was used on 13 occasions. External cephalic version was successful in 50 cases. There were no complications, but one baby died during labour from rupture of vasa praevia. The perinatal mortality rate of the series was 2 per cent, comparing favourably with a perinatal mortality rate of 3–6 per cent for breech delivery. The author recommends prophylactic external cephalic version without reservation.

Peter J. Huntingford

GYNAECOLOGY

386. **An Oral-Depot Estrogen: Physiologic Demonstration of Effect.**

By J. A. EPSTEIN, L. VOSBURGH, M. VESELL and H. S. KUPPERMAN. *Obstet. Gynec.*, **9**, 512–516. May 1957. 3 tables. 2 figs. 11 refs.

TACE (tri-*p*-anisyl-chlorethylene) is a synthetic oestrogen which has the physiological effects of oestrogens as well as the ability to be stored in the fat depots of the body and thence slowly released so that the ultimate effect is a prolonged one. It is more effective when given orally than parenterally. The prolonged, slow release of TACE from the body fat stores is said to prevent oestrogen-withdrawal bleeding.

A series of 31 patients with primary or secondary amenorrhoea exhibiting evidence of ovarian failure were given daily doses of TACE of 48 mg. for 4 weeks. On the 28th day of treatment 100 mg. progesterone in oil was injected intramuscularly and this dose of progesterone was repeated every 28 days without additional TACE therapy. The occurrence or absence of menses was considered to be a measure of the depot storage of oestrogen. The average prolongation of oestrogen effect beyond the period of TACE priming was 1·46 months. TACE was stored in the body from 0 to 4 months, with most patients storing for 1 to 2 months. Repeated courses in the same patient gave no predictable consistency of duration of response, and this limits to some extent the usefulness of the medication and the ease of management of the patient.

J. G. Dumoulin

387. **Congenital Adrenal Hyperplasia: Endocrine Patterns in Women and Effects of Cortisone Treatment.**

By R. R. DE ALVAREZ and E. K. SMITH. *Obstet. Gynec.*, **9**, 426–434. Apr. 1957. 8 figs. 10 refs.

The manifestations of hyperplasia of the adrenal cortex depend on the area of the adrenal gland involved and upon the age of the patient when the hyperplasia develops. Cushing's syndrome occurs if there is excessive secretion of glucocorticoids. The adrenogenital syndrome, characterized by progressive virilism, occurs if the hyperplasia causes excessive secretion of androgens. These cases have hirsutism, amenorrhoea, deepening of the voice and other signs of defeminization. If the hyperplasia develops in the female foetus, a female pseudohermaphrodite results. In 1950, Wilkins and co-workers

(*Bull. Johns Hopk. Hosp.*, **86**, 249) demonstrated the effectiveness of cortisone in suppressing androgen secretion, thus permitting feminization to occur.

Effective cortisone treatment of 2 young women with pseudohermaphroditism due to congenital adrenal hyperplasia is reported by the authors. The amount of oral cortisone required for suppression of the androgen secretion varied from 100 mg. daily in an 18-year-old girl to 37·5 mg. daily in a woman aged 34. Virilism was reversed and normal hormonal inter-relationships were established in each patient, resulting in menstruation, ovulation, and, in the older patient, pregnancy.

J. G. Dumoulin

388. **Differential Diagnosis of Hirsutism.** (Beitrag zur Differentialdiagnose des Hirsutismus.)

By J. Maršalek, M. Talaš, D. Novosad and L. Bartošová. *Arch. Gynäk.*, **188**, 443–456. 1957. 2 figs. 44 refs.

The authors classify hirsutism according to its aetiology into adrenocortical hirsutism, ovarian hirsutism and benign or familial hirsutism. Twenty-three patients with excessive hair growth were investigated gynaecologically, including endometrial biopsies and, in some cases, laparotomy for inspection of the ovaries. X-rays of the pituitary and perirenal air insufflations were carried out. Biochemical investigations included estimations of the B.M.R., blood cholesterol, sodium and potassium and blood sugar tolerance curves. Quantitative estimations of sebaceous gland secretions were also undertaken. Endocrine investigations included basal temperature charts and the determination of gonadotrophin, oestrogen, FSH, 17-ketosteroids and pregnandiol. Adrenal cortical function was tested by Thorn and Charvat's method. Cortisone tests were made, when 17-ketosteroid excretion was high, in order to differentiate between adrenal cortical tumour and hyperplasia.

(1) Adrenocortical hirsutism: Of the 23 patients tested 3 were found to be suffering from adrenocortical hyperplasia. In these cases the ovaries were normal and no changes were apparent in X-ray photographs of the sella turcica, the bones and the adrenals. 17-ketosteroid excretion was high with an increase in the second, third and fourth fraction on chromatographic separation. Excretion of oestrogen was at the upper limit of normal, pregnandiol excretion considerably increased. F.S.H. values were constantly low. B.M.R. and blood chemistry were normal except for low cholesterol values. The Thorn test showed a marked reduction of eosinophils.

(2) Ovarian hirsutism [Stein-Leventhal syndrome) characterized by enlarged, polycystic ovaries, failure of ovulation and menstrual disorders. The total 17-ketosteroid excretion was found to be normal, but there was an increase in the 4th and 5th fraction. Six of the 23 patients tested fell into this group.

(3) Familial hirsutism: This group comprised 14 patients who showed no gynaecological or biochemical abnormalities.

The differential diagnosis of hirsutism is facilitated by F.S.H. estimations (low in adrenocortical hyperplasia, normal in ovarian and familial hirsutism), 17-ketosteroid excretion (over 20 mg. in adrenocortical hyperplasia, normal in the other forms of hirsutism) and chromatographic fractionation of the 17-ketosteroid spectrum (3rd and 4th fraction increased in adrenal hirsutism, decreased in the first 3 fractions and increased in the 4th and 5th fractions in ovarian hirsutism, normal in familial hirsutism).

Erica Wachtel

389. **Amenorrhoea after Appendicectomy.** (Amenorrhoe nach Appendektomie.)

By H. Heiss. *Zbl. Gynäk.*, **79**, 927–933. 1957. 1 table. 16 refs.

During the years 1950 to 1955, 21 cases of amenorrhoea following appendicectomy were met with in the Gynaecological Department of the University of Graz. Fourteen were cases of acute appendicitis and 7 were chronic.

In the acute group post-operative amenorrhoea lasted 3 to 8 months. In 4 of these the right adnexa were found to be involved. Basal temperature records in this group never showed the normal bi-phasic curve and there were no fully developed secretory changes in endometrial biopsies obtained from these patients.

Amongst the seven chronic cases 5 gave a history of menstrual irregularity and it is notable that in these patients the inflammatory process always involved the right ovary. It would seem that chronic appendicitis has a particular influence on menstrual rhythm before and after operation. The duration of post-operative amenorrhoea in this group lasted 5 to 8 months. Endometrial biopsies showed no secretory changes and the bi-phasic curve did not appear in the basal temperature records.

Treatment consisted in improving the patients' general health. In addition, follicular and luteal hormones were used in various combinations depending on the histological appearances of the endometrium. Menstrual rhythm was restored in all patients.

Bruce Eton

390. **The Hazards of Intra-uterine Pessaries. An Evaluation.**

By R. W. Weilerstein. *West. J. Surg. Obstet. Gynec.*, **65**, 157–160. May–June 1957. 10 refs.

The author, from the Food and Drug Administration, circularized obstetricians in the Midwest and West of the U.S.A. asking if cases of injury resulted from the use of intracervical pessaries for the treatment of dysmenorrhoea or for contraception. One hundred and twenty-nine replies were received and indicated that pelvic sepsis, trauma and carcinoma occur so frequently following their prolonged use that the inescapable conclusion is that these pessaries, made of any material, have no place in modern medical treatment.

D. C. A. Bevis

391. **Nonsurgical Closure of Vesicovaginal Fistulas.**

By H. C. Falk and L. A. Orkin. *Obstet. Gynec.*, **9**, 538–541. May 1957. 1 table. 8 refs.

Small vesicovaginal fistulae with healthy surrounding tissue may heal completely after electrocoagulation if

postural drainage can be maintained for at least 10 days with an indwelling catheter. The authors proved this in 10 cases with only one failure. Four of the successes required 2 or 3 treatments.

Electrocoagulation was done under trilene analgesia using an electrode through a cystoscope. A Foley's catheter was inserted and the patient allowed home. She was instructed concerning continuous catheter drainage and advised to lie on her abdomen as much as possible. Sulphonamide therapy was given. The treatment was advised for fistulae 3 mm. in size or less.

J. G. Dumoulin

INFECTIONS OF THE REPRODUCTIVE ORGANS

392. **Present Day Problems of Genital Tuberculosis.** (Problèmes actuels posés par la tuberculose genitale.)

By E. RABAU and I. LIQUORNIK. *Gynéc. prat.*, **7**, 13–20. 1957. 6 refs.

The authors present their views on genital tuberculosis, basing their observations on a series of 106 cases seen at their hospital over the past 15 years. Of this number, 30 had adnexal tuberculosis, mostly verified by operation, and the rest showed endometrial tuberculosis on curettage. All the endometrial tuberculosis was found in women complaining of primary infertility.

In an earlier series of 200 infertile patients, the authors had found the incidence of genital tuberculosis to be 10 per cent; but in their present series of 3,000 cases of infertility the incidence of pelvic tuberculosis is only 4 per cent. They consider that this percentage will rise as antibiotics control the more usual causes of tubal blockage. In their cases which show tubal obstruction on X-ray examination, tuberculosis is responsible in 12 per cent of cases.

The usual age at diagnosis is between 20 and 35 years but the disease process starts much earlier, usually at puberty. Haematogenous infection of the pelvic organs with tuberculosis is probably rare, the most usual route of infection being direct spread from a peritonitis or a caseous mesenteric lymph node. The authors also consider the possibility that the exudate from a pleural effusion may traverse the diaphragm to reach the pouch of Douglas.

The main diagnostic step is curettage, although culture of the menstrual flow may reveal genital tuberculosis before it has spread to the endometrium. In view of the risk of activating a latent genital tuberculosis hysterosalpingography is preceded by curettage even although water soluble media are used.

The woman with genital tuberculosis is a potential source of infection to her husband and family, and on this ground alone the authors consider treatment essential. The possibility of reactivation of the tuberculous process is also to be considered. Treatment should be with streptomycin 1 gm. daily to a total of 60 to 120 gm., together with 200 mg. of INAH daily. Healing may cause scars and strictures in the tubes, predisposing to a subsequent ectopic pregnancy, and in an effort to diminish this scarring, the authors also give cortisone throughout the course of treatment, starting at 100 mg. and diminishing to 25 mg. daily. If an adnexal mass or hydrosalpinx persists after therapy, it should be removed surgically, but the authors suggest removal of only the tubes in order that menstruation may still occur. Even after streptomycin therapy, the chances of pregnancy are small. The authors have met two cases in which pregnancy occurred after a diagnosis of endometrial tuberculosis had been made. Both ended in abortion, one spontaneous, the other induced. No evidence of tuberculosis was found in the decidua and the placenta in either case.

Geoffrey Dixon

393. **Tuberculosis of the Pelvic Lymph Nodes and Carcinoma of the Cervix Stage O.** (Beckenlymphknotentuberculose und Carcinoma colli O.)

By K. RICHTER. *Geburtsh. u. Frauenheilk.*, **17**, 537–542. June 1957. 12 refs.

In order to investigate the frequency of tuberculous infection of the pelvic lymph nodes of apparently tuberculosis-free women, the author has studied the number of cases in which tuberculosis was found in nodes removed for the treatment of carcinoma of the cervix. There were 212 pelvic lymphadenectomies during the 9-year period beginning 1946 in the University-Frauenklinik, Graz, and the incidence of tuberculosis in these cases was 2·83 per cent.

In this article the author reports a further case of tuberculosis of the pelvic lymph nodes associated with carcinoma *in situ* of the cervix. A parous woman of 37 who complained of pain and malaise for a year, with intermittent fever, was found to have enlarged cervical and inguinal glands. She was shown at subsequent operation to have a small left haematosalpinx, matted groups of obturator and iliac lymph nodes, and enlarged hypogastric and para-aortic glands. X-ray of the chest showed inactive apical lesions; there was no evidence of bony, intestinal or renal tuberculosis.

A cervical smear showed malignant squames and subsequent biopsy showed pre-invasive cancer. No evidence of endometrial tuberculosis was found on curettage.

After a course of P.A.S., streptomycin and isoniazid, total hysterectomy, left salpingo-oöphorectomy and right salpingectomy were performed. On histological section the left tube showed non-specific chronic inflammatory changes. The uterus and tubes were free from cancer and tuberculosis. Section of a hypogastric lymph node showed caseating masses with a few areas of granulation tissue undergoing fibrosis. There was no evidence at operation of tuberculosis of any other abdominal organs. The patient was well a year later.

[Granulomatous changes in the regional lymph nodes of a "tuberculoid" or "sarcoid" type, resembling the histological picture in the gland biopsied in this case, have been reported in association with carcinoma on several occasions. The granulomatous changes in these cases have been considered to be the result of absorption of irritant material from the tissues drained by the affected lymph nodes, and not the manifestation of a granulomatous infection (Symmers, W. St. C., *Amer. J. Path.*, 1951, **27**, 493).

In none of the author's cases has the diagnosis of tuberculosis of the pelvic lymph nodes been confirmed bacteriologically. In view of this, his assumption that the histological picture of tuberculosis in the pelvic lymph nodes of patients suffering from carcinoma of the genital tract can be used as an index for assessing the incidence of pelvic tuberculosis in the female, is suspect.]

Peter J. Huntingford

394. **Oral Treatment of Trichomonas Vaginitis with Aminitrozole.**

By J. BARNES, A. BOUTWOOD, E. HAINES, W. LEWINGTON, E. LISTER and B. J. HARAM. *Brit. med. J.*, **1**, 1160–1162. May 18, 1957. 2 tables. 5 refs.

The authors, from the Elizabeth Garrett Anderson Hospital, London, have made a controlled trial of oral treatment of trichomonal vaginitis, using aminitrozole (tritheon).

Patients with trichomonal vaginitis were divided into two groups. The treated groups received aminitrozole 100 mg. three times daily by mouth for 10 days, and aci-jel vaginal jelly inserted night and morning for 3 weeks. The control group received treatment by aci-jel only.

Of 37 patients who received treatment with aminitrozole and aci-jel, only 6 were cured of trichomonas vaginitis. Twelve of the treated groups had one course of aminitrozole, six had two courses, and seven had three courses.

The results were so disappointing that the authors abandoned the trial.

They also record attempts to culture the *Trichomonas vaginalis*, using the simplified trypticase serum medium of Kupferberg.

About 40 per cent of those preparations which revealed large numbers of trichomonads in the hanging drop were still positive after 48 hours' cultivation, but with sluggish motility and reduced numbers. The authors felt that the medium encouraged the protozoa to survive for a limited period, but did not promote their growth. A thorough examination with the hanging drop method seemed a far more reliable guide, and culturing was discontinued.

Eileen Wilson

395. **The Treatment of Resistant and Recurrent Trichomonas Vaginitis and Preventive Measures Against Re-infection.** (La thérapeutique de la vaginite à trichomonas résistante et récidivante, et les mesures préventives contre la réinfection.)

By B. STAMBOLOVIC and M. KRANJCIC. *Gynéc. Obstét.*, **55**, 526–532. Nov.–Dec. 1956. 1 fig. 7 refs.

The writers state that trichomonas infection is now comparatively rare whereas in the past it concerned every third patient. In the first half of 1953 amongst patients suffering from various gynaecological complaints 209 also showed trichomonas infection. In the second half of 1953 there were 133 cases. In the first half of 1954 the number had diminished to 92, and in the second half of 1954 to 52, although the number of gynaecological patients had increased.

In their opinion trichomonas infection confined to the vagina is easily cured with vaginal suppositories (made by Pliva of Zagreb, Yugoslavia) containing a non-toxic mercury derivative. The small number of recurrences were due to re-infection from another member of the family, or from trichomonas infection of the bladder, kidneys, cervix, Bartholin's or Skene's glands. In the two years concerned, 486 trichomonas infections of the vagina were treated. Amongst these 52 showed a trichomonas infection of the bladder, demonstrated by direct examination of the centrifuged catheter urine.

The treatment advised in these cases constituted insertion for five days running of mercurial suppositories into the vagina, on the five days following this the patient has a lysol douche, and during the course of this treatment 20 ml. of 0·5 per cent albargin (a silver preparation manufactured by Hoechst of Frankfurt, Germany) are instilled into the bladder on alternate days by catheter and retained for at least two hours.

In certain of the bladder cases, recurrence took place. Aureomycin by mouth was found to be useless. In several cases catheterization of both ureters was carried out and 0·5 per cent albargin instilled with good effect.

Many searches were made for evidence of trichomonas endocervicitis in resistant cases, but the writers only found four cases. Treatment of these was by vaginal irrigations of 50 per cent zinc chloride, vaginal tablets of an arsenical preparation (Fluorsan, made by Pliva of Zagreb, Yugoslavia), and the application of the silver nitrate stick to the cervical canal. This third procedure is carried out under the cloak of penicillin and sulphonamides.

In the writers' opinion there are rare cases of infection of Skene's and Bartholin's glands, but they were unable to prove this even after aspiration of the secretion in suspected cases with a syringe and blunt needle.

As regards prevention, not only the husband but also all female members of the family must be examined to exclude carriers. In the husband examination of urethral smears following prostatic massage is essential. A course of 32 capsules of aureomycin or terramycin is advised—one to be taken every six hours. In refractory male cases, bladder instillations of 0·5 per cent albargin are advised once daily for ten days, following prostatic massage. Twelve such cases were treated by the writers.

Further precautions were found necessary in the way of treating all these trichomonas cases, once diagnosed, by isolation in the gynaecological department.

D. Maxwell

NEW GROWTHS OF THE REPRODUCTIVE ORGANS

396. **Basal-Cell Carcinoma of the Vulva: Review of the Literature and Report of a Case.**

By R. W. A. NEL. *S. Afr. med. J.*, **31**, 381–383. Apr. 20, 1957. 21 refs.

A case of basal-cell carcinoma of the vulva in a 36-year-old patient is described. She gave a 2½ years history of a slow growing lump to the left of the clitoris. The nodule, about ½ inch in diameter, was excised.

The incidence in numerous series presented varied from 1·28 per cent to 12·5 per cent of all carcinomas of the vulva. The tumour is generally believed to originate in the basal cells of the epidermis, but many other theories have been put forward. The 2 clinical types found on the vulva are the nodular-ulcerative type and the superficial flat basal-cell epithelioma. A third type presenting with basal-cell carcinoma in one area and squamous-cell carcinoma in another has been described. Basal-cell carcinoma rarely metastasizes. Growth is slow and it extends locally. Review of the literature reveals about a dozen proved cases of metastases of pure basal-cell carcinoma, but some authors believe that in these the diagnosis was erroneous. The histology is discussed.

The onset is insidious, and years often elapse before an opinion is sought. The average age is given as 63 years, and patients complain of a lump, a "sore", recurrent itching, pain, bleeding or burning on micturition. The lesion is generally on the labium majus. Diagnosis should be made by biopsy and free excision. Numerous methods of treatment are discussed. The author concludes that wide local excision is the treatment of choice. In the basi-squamous type radical surgery is indicated. Prognosis is difficult to assess as it occurs in the age group in which life expectancy is not long. The tumour seems to recur rather than metastasize. Many sections should be studied to exclude squamous cell elements.

L. J. Abramowitz

397. **Granular-Cell Myoblastoma of the Vulva and Lower Respiratory Tract: Report of a Case.**

By N. E. Chiodi, I. A. Siegel, P. F. Guerin and D. McCaughan. *Obstet. Gynec.*, **9**, 472–480. Apr. 1957. 3 tables. 5 figs. 49 refs.

Granular-cell myoblastoma is an uncommon tumour. Its occurrence in more than one site in any patient is very rare. The authors report a case of a 22-year-old girl who had a tumour in the labium majus and also one blocking a main bronchus in the lower lobe of the lung. Both were removed surgically.

A review of the literature shows that 350 cases of granular-cell myoblastoma have been recorded (19 arising in the vulva), and in only 12 was the lesion multiple. The majority of the tumours show no tendency to metastasis but are locally invasive because of the absence of a capsule. Wide local excision is the method of treatment.

J. G. Dumoulin

398. **Vaginal Metastases from Carcinoma of the Cervix and Corpus Uteri.** (Vaginalmetastasen beim Kollum- und Korpuskarzinom.)

By D. Buttenberg and H. Zeitz. *Geburtsh. u. Frauenheilk.*, **17**, 427–434. May 1957. 3 tables. 10 refs.

Ninety-two cases of vaginal metastases in association with primary carcinoma of the cervix or corpus uteri, occurring in the period 1935–1953 at the University Frauenklinik, Heidelberg, are analyzed.

Of 2,049 cases of carcinoma of the cervix 2·9 per cent had deposits in the vagina; and of 618 cases of carcinoma of the corpus uteri 5·2 per cent had vaginal secondaries. The incidence is compared with other series in the literature. There are marked discrepancies, mainly accounted for by the selection of cases and the definition accepted for a vaginal secondary. All, however, agree that the incidence of secondary vaginal deposits is higher in carcinoma of the corpus uteri than in carcinoma of the cervix.

In this series deposits were present in 15 cases of carcinoma of the cervix and 14 cases of carcinoma of the body at the time of treatment of the primary tumour.

The authors believe that diagnostic curettage and biopsy, vaginal packing necessary to the insertion of radium, and especially the clamping and other manipulations at hysterectomy, are responsible for opening up the pathways for retrograde lymphatic and venous emboli of tumour particles. Three-quarters (45 cases) of the deposits occurring in association with carcinoma of the cervix were found after treatment. Operative treatment of carcinoma of the body of the uterus was particularly associated with vaginal metastases. Of 18 cases in which deposits appeared after treatment, 15 had been operated on and 3 had been given radium. In contrast, the ratio of operation to radium treatment of carcinoma of the corpus uteri in the Heidelberg clinic was 1:1. It is not the policy of the authors to use post-operative radium to the vaginal vault.

Eight cases of the series were not treated because of generalized metastases, 76 cases were treated with local applications of radium, and the rest were treated either with coagulation diathermy or a linear accelerator. There was a 15 per cent five-year cure rate in those cases of vaginal secondaries with carcinoma of the cervix, and a 21·9 per cent five-year cure rate in those with deposits arising from carcinoma of the corpus uteri. The authors recommend the use of X-irradiation of the inguinal lymph nodes, as well as treatment of the vaginal metastases.

Peter J. Huntingford

399. **Uterine Adenoacanthoma.**

By E. Novak and W. B. Nalley. *Obstet. Gynec.*, **9**, 396–402. Apr. 1957. 1 table. 5 figs. 15 refs.

Squamous metaplasia is found far more frequently in the uterine cervix than in the corpus, but it may occur in the endometrium, and in benign as well as malignant conditions. It is the basic endometrial pattern and not the squamous metaplasia that is important in formulating prognosis.

Uterine adenoacanthoma is a variant of endometrial cancer, and this term should be restricted to malignancies in which there are major degrees of acanthosis. There were 16 cases at Johns Hopkins Hospital during 1943–53, and all showed features associated with adenocarcinoma, such as a high percentage of obesity, hypertension and diabetes, but the average age was 45, ten years younger than the average for adenocarcinoma. In 15 of the cases, there was no myometrial invasion and there were no distant metastases. Most of the cases were treated by hysterectomy, with or without previous

irradiation. In the sixteenth case, the tumour exhibited unquestionable malignant properties of both epidermoid and glandular elements. The tumour involved adnexa, omentum and regional nodes, and a rapid fatal outcome ensued.

Thus, 15 of the 16 cases showed a low grade malignancy, and this comparatively innocuous behaviour is found in similar lesions of the ovary. The authors suggest that the finding of well-differentiated squamous cells in adenoacanthoma means that the prognosis is much better than in the ordinary type of adenocarcinoma.

J. G. Dumoulin

400. **Occult Carcinoma and Premenopausal Abnormal Uterine Bleeding.**

By J. N. MILLER and R. C. BENSON. *West. J. Surg. Obstet. Gynec.*, **65**, 126–129. May–June 1957. 9 refs.

The authors, at the University of California, have studied the incidence of carcinoma in patients under 50 with abnormal bleeding; patients with visible lesions of the cervix and with possible complications of pregnancy have been excluded. Six hundred and forty-seven patients were examined in 5 years and 12 cervical carcinomas and 8 adenocarcinomas of the endometrium were discovered on curettage. Although vaginal smears were invaluable when available, the authors conclude that examination under anaesthesia and diagnostic curettage must always be employed in these cases, but that major therapy must be postponed until all pathological reports are complete, otherwise the patient may be subjected to unnecessary or inadequate procedures.

D. C. A. Bevis

401. **Vaginal Cytology in Menopausal Women with Benign and Malignant Neoplasms.** (Das Scheidenabstrichbild in der Menopause bei gut- und bösartigen Neubildungen.)

By G. WASCHKE. *Zbl. Gynäk.*, **79**, 909–915. 1957. 13 tables.

This investigation was prompted by the observation made by other workers that vaginal smears show evidence of oestrogenic stimulation in menopausal women with carcinoma of the corpus.

The author confirms these findings in a series of vaginal smears of menopausal women seen in the Department of Obstetrics and Gynaecology of the City Hospital, Berlin-Spandau. Thirty per cent of the cases were excluded: women with vaginitis or genital prolapse, those wearing pessaries, those who had previously undergone surgical or radiation menopause and women who had had vaginal douches before the smears were due to be taken. This exclusion left a series of 199 women who were at least 3 years past the menopause.

Vaginal smears showing oestrogenic effects were seen in 3 out of 68 women in whom pelvic examination did not reveal any abnormality; in 9 out of 63 patients with benign neoplasms; and in 6 out of 13 patients with carcinoma of the corpus uteri. In 36 patients with extragenital, mammary, ovarian and tubal cancers, there was no significant incidence of vaginal smears showing oestrogenic activity.

Bruce Eton

402. **Carcinoma of the Cervical Stump.** (Das Zervixstumpfkarzinom.)

By W. FINK. *Zbl. Gynäk.*, **79**, 782–789. 1957. 5 tables. 30 refs.

The author reports on 59 cases of stump carcinoma amongst 2,126 cervical cancers observed between the years 1945 and 1956 at the Gynaecological Clinic, Dresden-Friedrichstadt, an incidence of 2·77 per cent. Fifteen cases occurred within a year, and more than half of the total within four years of sub-total hysterectomy. The longest interval was 30 years. Eleven of the patients were nulliparae.

For routine treatment radium and X-rays were used. The cervical stump was removed surgically in only 5 patients. The cases arising during the years 1945 to 1951 allowed an assessment of the five-year cure rate (18·5 per cent). This unfavourable result is attributed to the poor general health of the patients during the early post-war years and a predominance of Stage II and III cancers. Owing to heavy strain on the facilities of the radiotherapy departments treatment was often delayed for 8 to 12 weeks.

The author adduces the arguments for and against total and sub-total hysterectomy and concludes that the total operation should be the procedure of choice, especially in women over 43 years of age.

Bruce Eton

403. **The Value of Histological Investigation of the Parametrium in Surgical Specimens Removed for Carcinoma of the Cervix, With Regard to Ascertaining the Degree of Spread.** (Die Wertung der histologischen Untersuchung der Parametrien beim Kollumkarzinom im Hinblick auf die Feststellung des Ausbrietungsgrades.)

By K. H. BRUNTSCH. *Geburtsh. u. Frauenheilk.*, **17**, 518–523. June 1957. 1 table. 3 figs. 8 refs.

Dr. Bruntsch discusses the relationship between clinical assessment of parametrial spread from carcinoma of the cervix and the histological findings. The material obtained from 115 radical vaginal operations for carcinoma of the cervix performed in the University Frauenklinik of the Free University of Berlin since 1953, has been examined histologically, special attention being paid to the parametrium. Serial sections of the parametrium immediately next to the uterus and on the lateral pelvic wall were studied. There was histological evidence of invasion in 25 cases, unilateral in 20 cases and bilateral in 5 cases.

In only a few instances was there a wide front of invasion, and in these cases, it was accompanied by severe inflammatory infiltration, mainly of lymphocytes and plasma cells. In most cases the spread took the form of small isolated deposits, which were usually microscopical and unaccompanied by any inflammatory reaction.

A comparison is made between the clinical and histological findings. In 71 patients the parametrium was clinically free from metastases. Eleven of these were found to be positive histologically, although the secondary deposits were always small. Only in 14 cases out of 44 in which parametrial spread had been diagnosed

clinically, was this confirmed microscopically. In 18 cases there were inflammatory changes, which could have been confused clinically with carcinomatous deposits, but in the remaining 12 cases no histological explanation was found for the clinical assessment.

The author is of the opinion that in many cases of carcinoma of the cervix, the staging is too high, and that this is mainly due to inflammatory infiltration of the parametrium. Because of this he considers that statistics relating to the treatment and follow-up of carcinoma of the cervix are misleading. He recommends, not that the clinical staging be altered, as this would invalidate any comparison made with series of cases treated by radiotherapy alone, but that the histological staging should be noted and taken into account in the analysis of cases.

Peter J. Huntingford

404. **Primary Ovarian Adenoacanthoma: Its Relationship to Endometriosis.**

By J. D. THOMPSON. *Obstet. Gynec.*, **9**, 403–416. Apr. 1957. 5 tables. 5 figs. 43 refs.

Malignant change in ovarian endometriosis has been shown to occur by several authors, but it is very rare. The author concerns himself with the relationship of endometriosis to a particular type of ovarian carcinoma, the adenoacanthoma. In the 20 proved cases in the literature of malignant transformation of ovarian endometriosis, 9 are adenoacanthomas.

The material for this study is taken chiefly from the files of the Ovarian Tumour Registry and includes 17 cases of primary ovarian adenoacanthomas, of which 10 were considered to arise from ovarian endometriosis, and possibly 3 others, for in only 4 cases was there no associated endometriosis.

It would seem that ovarian adenoacanthomas arise most frequently from ovarian endometriosis. The former are similar to uterine adenoacanthomas and have a low degree of malignancy and a good prognosis.

J. G. Dumoulin

405. **Post-radiation Nephritic Syndrome: Report of a Case.**

By J. H. ZEIGERMAN, E. G. TULSKY and P. MAKLER. *Obstet. Gynec.*, **9**, 542–548. May 1957. 4 figs. 7 refs.

A case is reported of serous cystadenocarcinoma of the ovary in a 17-year-old girl with a 10-year survival following total hysterectomy and bilateral salpingo-oöphorectomy plus external radiation therapy. The abdominal cavity was irradiated with a tissue dose of 1,100 r through 4 anterior and 4 posterior 10×15 cm. portals.

The clinical picture in recent years suggests that a post-radiation nephritis has supervened. This condition usually shows a latent period averaging about 8 months before the onset of renal damage. The patient then begins to complain of dyspnoea, headaches, oedema and lassitude. Hypertension and anaemia are found. Albuminuria, microscopic haematuria and an elevated blood urea may occur. Death from uraemia may follow, or there may be some recovery with the judicious use of blood transfusions and prolonged rest; with a residual chronic nephritis.

If radiotherapy is used in this type of case, protection of at least one-third of the renal tissue from the radiation should be the aim. The use of radioactive colloidal gold instilled intraperitoneally would be a better method of treatment today.

J. G. Dumoulin

406. **Endometrial Mitoses.** (Mitosen im Endometrium.)

By C. AHRENS and G. PRINZ. *Geburtsh. u. Frauenheilk.*, **17**, 475–483. May 1957. 12 figs. 34 refs.

From material obtained in the Frauenklinik, Hamburg, the authors have studied the number and type of cell mitoses in endometrium in the different phases of the normal menstrual cycle; and the relationship between the number and type of cell mitoses occurring in endometrial hyperplasia and adenocarcinoma of the endometrium.

Sections were taken from 30 normal cases, from 30 cases of cystic glandular hyperplasia and from 30 cases of carcinoma of the corpus uteri. Sections 4 microns thick were cut and stained with haematoxylin and eosin. The number, type and situation of the mitoses in 100 microscopic fields of each section were noted (magnification times 1,600). The tissue unit studied in each case measured 3·16 by 10^{-8} c.mm.

Meyer's nomenclature for the menstrual cycle is used. Mitoses were first seen on the sixth post-menstrual day. The highest number seen (average 29·9) was in the early proliferative phase. In the late proliferative phase the number dropped to 16·2. There was a further drop to an average of 2 in the secretory phase and 1·8 in the pre-menstrual phase. None of these mitoses was abnormal. During the proliferative phase most of the mitoses were in the epithelium and in the secretory phase they were mainly found in the stroma.

In cystic glandular hyperplasia the mitoses were for the most part normal and the average number was 7·5.

Mitoses were graded as normal, irregular or pathological. The irregular form does not necessarily imply that malignant change is imminent, although the authors confirm the reports of others that irregular forms are not as common in normal tissue as in carcinomatous tissue.

The average number of mitoses in atypical hyperplasia was 27·5, most of which were in the epithelium. Occasional pathological forms were seen.

In the case of carcinoma half the mitoses were pathological and they were irregularly distributed between the stroma and the epithelium. The average number of mitoses was 45·5.

The authors conclude from these studies that atypical hyperplasia is neither pre-cancerous, nor can it be compared with carcinoma *in situ* of the cervix. Study of endometrial mitoses, in their opinion, lends no proof to the theory of a continuous process of gradual transition from hyperplasia to adenocarcinoma.

Peter J. Huntingford

407. Endometrial Lavage as an Aid in the Diagnosis of Carcinoma of the Endometrium.

By D. G. MORTON, J. G. MOORE and N. CHANG. *West. J. Surg. Obstet. Gynec.*, **65**, 113–123. May–June 1957. 16 figs. 5 refs.

The authors, from the University of California, have modified the Hecht technique of aspiration biopsy. The cervix is exposed, wiped and then 3–4 ml. of sterile saline gently injected into the uterine cavity through a fine cannula; the fluid is allowed to drain into the posterior fornix, is aspirated into the syringe, centrifuged and the sediment placed on a slide treated with egg albumin. The cells are fixed in an ether-alcohol solution and if blood-stained are washed with N/10 HCl for one minute and then returned to the fixative. Staining is by the Papanicolaou technique and the criteria for diagnosis of malignancy are those described by Papanicolaou and Traut. No complications have been recorded following the procedure although a few patients suffered from mild and transitory cramps.

Altogether 797 specimens have been examined from 673 patients and carcinoma diagnosed 26 times. There were 4 false positives and 2 false negatives. In addition there were 25 carcinomas of the cervix but as was expected, the usual cervical smear was more useful in these cases. The authors conclude that the procedure is simple and accurate enough to warrant a further trial.

In a discussion of this paper, H. F. Traut points out that endometrial cells are shed in clumps and must not be overstained if they are to be easily examined. He agrees that the method is worth further study.

D. C. A. Bevis

408. The Problem of Endometriosis. (Zur Frage der Endometriose.)

By M. FRIZ. *Zbl. Gynäk.*, **79**, 826–832. 1957. 25 refs.

The author reports the result of his clinical studies of 113 cases of endometriosis. They represent an incidence of 8·3 per cent amongst 1,353 patients who underwent operations at the Gynaecological Clinic of the City of Heilbronn between 1953 and 1956.

The age of the patients ranged from 24 to 55 years (average age 41·1 years). Uterine adenomyosis was not encountered in nulliparous women. In 32 patients the diagnosis of endometriosis was made before operation, usually on account of pain.

During the period under review 112 hysterectomies were performed for the treatment of severe menopausal metrorrhagia. On histological examination of the myometrium internal endometriosis was found in 14 of these.

There were also foci of endometriosis in 52 fibromyomatous uteri.

The author gives an account of various conservative and radical surgical procedures used in the treatment of these patients. Although the post-operative follow-up did not exceed 12 months, he concludes that there is a place for conservative surgery in the treatment of external endometriosis.

Bruce Eton

409. Carcinoma Arising in Endometriosis: Report of Two Cases.

By J. W. GREENE, JR., and H. T. ENTERLINE. *Obstet. Gynec.*, **9**, 417–421. Apr. 1957. 7 figs. 10 refs.

Two cases are reported of malignant change in endometriosis. One was a case of adenocarcinoma and one of adenoacanthoma. The authors state that this brings the total number of reported cases to 24.

J. G. Dumoulin

410. Endometriosis in the Vaginal Scar Following Hysterotomy for Therapeutic Abortion. Report on 100 Cases.

By T. GOTTLIEB. *Acta obstet. gynec. scand.*, **36**, 194–208. 1957. 7 figs. 52 refs.

The author, writing from Stockholm, has been able to observe 100 patients suffering from endometriosis following vaginal hysterotomy for therapeutic abortion. Twenty-eight of the patients had no complaints; of the remainder, 61 complained of dysmenorrhoea, 32 of dyspareunia, and 36 of dysuria. The first symptoms did not generally occur until several years after the operation. In almost one half of the cases examination with a vaginal speculum showed bluish cysts on the anterior aspect of the uterine cervix; in the remaining cases there were tender areas of infiltration at the front of the cervix, and moderate pressure on these areas reproduced the pain complained of; in 12 cases the presence of endometriosis was confirmed on cystoscopy.

Biopsy was done on 87 patients, including all those in whom bluish cysts were not seen on examination with a speculum. Sixty-seven times the pathologist reported "endometriosis", 11 times "suggested endometriosis", in 8 cases the picture could "not be said to be typical of endometriosis in all respects", and in the remaining case there was "no endometriosis". Fourteen patients who suffered discomfort and had widespread lesions were treated by conservative surgery; 10 of them became free of symptoms, 2 had recurrences, 1 was operated on shortly before the paper was submitted for publication, and 1 died following the operation. Local androgenic therapy (with perandren crystules) was given to 25 patients, 18 of whom became free of symptoms.

[No information about the incidence of this complication was obtained as there was no systematic follow-up of all patients who underwent vaginal hysterectomy. Even if one makes allowance for possible errors in diagnosis, the number of the cases reported is surprising, unless the total number of vaginal hysterotomies for termination of pregnancy was large.]

N. Alders

411. The Value of Irradiation Therapy in the Treatment of Endometriosis.

By A. BROSSET. *Acta obstet. gynec. scand.*, **36**, 209–225. 1957. 6 figs. 56 refs.

The hospital records of the cases of endometriosis treated by irradiation in the gynaecological department of the Radiumhemmet in Stockholm were studied. The essential features of X-ray therapy in endometriosis are to fractionate the treatment and to deliver a dose of 100 to

150 r to the lesion from 2 or more portals. The working conditions were: 180 Kv., 15 Ma., 50 cm. focus-skin distance, and 0·5 mm. Cu. +1 mm. Al. filter. In cases of extragenital endometriosis the palpable lesion only was irradiated.

The cases numbered 101 and were divided into 3 groups. (*i*) Endometriosis involving the ovaries, (*ii*) endometriosis involving the recto-vaginal septum, (*iii*) endometriosis elsewhere. Of 84 cases in which the records provided evidence that the diagnosis was correct, 69 patients were symptom free or improved following irradiation therapy. In 55 cases the menstrual cycle was re-established following a period of amenorrhoea of varying length, in 19 lasting amenorrhoea resulted, and in 10 cases there was amenorrhoea before treatment because of a previous hysterectomy.

The series also included a few cases of endometriosis in the scar following vaginal hysterotomy for termination of pregnancy, and in which radium was directly applied to the lesion through the vagina.

The author concludes that there is justification in using radiation therapy on a larger scale than has hitherto been done in the treatment of endometriosis in which operation presents difficulty.

N. Alders

OPERATIONS

412. **Cytologic and Histologic Correlation of Colposcopic Findings.**

By W. R. Lang, A. E. Rakoff and G. Tatarian. *Surg. Gynec. Obstet.*, **104,** 717–721. June 1957. 2 figs. 4 refs.

This is an effort to explore the relationship of the 3 investigative methods of colposcopy, cytology and biopsy and is based on 3 years experience during which approximately 1,000 colposcopic examinations have been performed at the Jeffreson Medical College and Hospital, Philadelphia.

A number of normal and abnormal colposcopic appearances are clearly described and are discussed in relation to the corresponding cytological and histological findings.

The authors conclude that in the early detection of cancer, cytology and colposcopy reach their maximum of efficiency when employed together but they consider that biopsy is still mandatory before treatment is undertaken.

John P. Erskine

413. **Total or Subtotal Hysterectomy? Contribution to the Incidence of Stump Carcinoma and its Prevention.** (Totale oder subtotale Hysterektomie? Ein Beitrag zur Frage der Frequenz des Stumpfcarcinoms und seiner Prävention.)

By A. Árvay, G. Báló and C. B. Rozgonyi. *Arch. Gynäk.*, **188,** 391–410. 1957. 9 tables. 1 fig. 55 refs.

In view of their results with 1,176 hysterectomies carried out during the last 5 years the authors state:

(1) That they prefer vaginal hysterectomy to total abdominal hysterectomy, if the uterus is mobile, the vagina wide enough, the fibroid not bigger than a fist and the adnexa normal. 34·4 per cent of all hysterectomies carried out in the last year were done *per vaginam*.

(2) When there is an indication to remove the uterus, total hysterectomy is the treatment of choice. 54·7 per cent of all hysterectomies were total abdominal hysterectomies.

(3) Subtotal hysterectomy was carried out in patients who were poor operational risks or in whom total hysterectomy would have been technically difficult, also for teaching purposes. Prior to operation, vaginal smears, cervical biopsy and colposcopy were carried out. Subtotal hysterectomies constituted 10·8 per cent of all hysterectomies.

Of the 1,176 hysterectomies performed 809 were carried out for benign conditions. Total hysterectomy carried no greater operative mortality and no greater risk of operative and post-operative complications than subtotal hysterectomy. The mortality rate of the total hysterectomies (including total hysterectomy for malignant conditions) was 0·98 per cent in 507 cases, of the subtotal hysterectomies 1·8 per cent in 333 cases. There was no death in 336 cases of vaginal hysterectomy.

Of the 331 women followed up after subtotal hysterectomy 7 or 2·11 per cent developed carcinoma in the cervical stump. Of all cases of cervical cancer observed in 10½ years 2·7 per cent were stump carcinomas. In order to prevent the occurrence of stump carcinoma the authors recommend the practice of total hysterectomy; if this is impractical, cervical biopsy and conization, cytological and colposcopic examinations at regular follow-up clinics are recommended.

Erica Wachtel

414. **An Analysis of One Hundred and Five Radical Hysterectomies at the Free Hospital for Women.**

By R. W. Kistner and C. J. Duncan. *Surg. Gynec. Obstet.*, **104,** 733–745. June 1957. 12 tables. 16 refs.

This is a report on yet another series of cases of carcinoma of the cervix treated by radical hysterectomy, on this occasion at Brookline, Massachusetts during the years 1943–1953.

The analysis follows the general pattern of its predecessors but a post-operative surgical and pathological classification is utilized in addition to that recommended by the League of Nations. A careful selection of cases suitable for surgery has been made and the 105 patients discussed represent only 19·4 per cent of the total number of cancers of the cervix treated during the 11-year period. Eighty-five patients were classified according to the League of Nations Classification as Stage I and 20 patients as Stage II.

Prophylactic anticoagulants and antibiotics were given routinely, and radium was administered preoperatively to 74 of the patients with the hope that implantation of tumour cells at the time of surgery would be diminished. Twenty-seven of these 74 patients had no residual tumour in the cervix at the time of hysterectomy and all are living without apparent disease 4–8 years post-operatively.

The operative mortality was 1, 44 of the 105 patients were classified as morbid and 7·6 per cent developed urinary fistulae. The 5-year cure rate in Stage I cases was 81·1 per cent.

The prognostic importance of lymph node involvement is demonstrated and it is considered that in this event post-operative X-ray therapy is of value in increasing survival.

John P. Erskine

415. **Conservative Surgery of the Ovary.** (La chirurgia funzionale dell'ovaio.)

Minerva ginec., Torino, **9**, 345–407. May 15, 1957.

This number is composed of a series of papers on this subject by various workers, with many illustrations, tables and references. Conservation of the ovary is a prime aim in all cases where the organ is not affected with gross cystic or malignant disease, except in elderly women in whom its function has become obsolete. Even in the latter one cannot exclude its influence in preventing undue atrophy of the vaginal and vulvar mucous membrane. At the same time, certain conditions of the ovary call for intervention in younger women, as for example scleromicrocystic disease (polymicrocystic dystrophy) in its various forms, ovaries incarcerated by tubal or peritoneal inflammation, endometriosis, or painful prolapsed ovaries often associated with varicoceles of the infundibulo-pelvic ligaments. After total ablation of such functioning ovaries, hormonal substitution therapy by implantation of tablets or oral administration of oestrogens has not proved a complete answer. The two commonest varieties of such small cystic ovaries are due (1) to tumultuous maturing of many follicles without their dehiscence, or (2) to prevention of rupture of normally ripening follicles where the free abdominal surface of the ovary is sealed off by an adherent tube and broad ligament resulting from salpingitis. Whilst the second group is palpably due to local causes in most cases, the first is bound up with abnormal stimuli arising from the pituitary (hyperprolanaemia). Polymicrocystic dystrophy is a common cause of sterility and anovular menstruation. Medical measures to try to control such types of irregular menstruation by administration of various hormones have often been found to aggravate these conditions and to inaugurate or increase any pain accompanying them.

Measures of conservative surgery proposed for scleromicrocystic ovaries include (1) thorough ignipuncture of the ripening and atretic follicles, (2) "curettage" by longitudinal deep splitting of the ovary from its free edge and extensive scraping of the parenchyma followed by re-suturing of the two halves, (3) resection of up to four-fifths of the whole ovary, (4) suturing of omentum to the ovary to obtain partial portal vascular drainage of the ovary, the idea being that the vicious circle can be broken by destruction of follicular hormone in the liver before it can react upon the pituitary. [It would appear very difficult to regulate the amount of shunt obtained by this means.] (5) Immediate grafting of thin slices of (removed) ovary into an vascular extraperitoneal space, preferably in the anterior abdominal wall where it can be kept under some sort of observation. These grafts are said to remain active for some months and to lose their hormonal influence only gradually. This measure is recommended where the ovaries have been inevitably removed together with the tubes for diseases of the latter, or in the course of operations for endometriosis, (6) tying off the ovarian artery, although it is known that the arterial blood supply is most variable and anastomoses with tubal and uterine branches are frequent but unreliable, (7) measures aimed at denervation of the sympathetic coats of the ovarian arteries, or at the hilum, including even the injection of chemicals.

In dealing with prolapsed ovaries or when there are any conditions likely to cause adhesions behind the uterus, the ovary should be stitched to the round ligament or to the peritoneal reflexion between bladder and uterus, either with catgut if only a temporary displacement is needed, or permanently with silk. Partial or complete ablation of the pouch of Douglas is another step which may be helpful, and others worth consideration are shortening of the infundibulo-pelvic fold and tying off of varicosities of the ovarian veins.

To obtain the best subjective results it is recommended that all the above measures be combined with resection of the pre-sacral nerve; indeed this step is regarded as an essential one when pre-operative symptomatology has included pelvic pain.

W. C. Spackman

416. **Partial Resection of the Ovaries.** (Resection partielle des ovaires.)

By W. P. PLATE. *Gynéc. prat.*, **7**, 9–12. 1957.

The place of resection of the ovaries in gynaecology is considered. Two cases in which amenorrhoea was accompanied by hirsutism are presented in detail. In both cases resection of one- to two-thirds of the ovaries was followed by a return of regular menstruation, and in one case by pregnancy.

In the author's clinic the operation has been carried out on 77 women. Seventy-two of these patients were complaining of disordered menstruation; 66 had been followed up. Thirty-six regained a normal menstrual rhythm; and of the 47 who had had anovulatory cycles 27 showed ovulation post-operatively. Thirty-three of the patients were married and of these 7 have become pregnant since operation. Hirsutism was present in 42 of the 77 cases. There was complete relief in 1 case and improvement in 7. In the remainder, no change occurred.

The author believes that partial resection of ovaries should be carried out in cases showing anovulatory cycles and in cases of amenorrhoea in which the endometrium is proliferative or shows a cystic glandular hyperplasia. The operation may be of use in grossly irregular cycles.

Before undertaking partial resection, a full endocrinological investigation must be carried out. This must

show a normal excretion of gonadotrophins and oestrogens and a normal or only slightly elevated excretion of 17-ketosteroids. Thyroid function should also be normal. Hirsutism alone is not an indication for operation; but on the other hand, operation should be undertaken when indicated even though the ovaries are not palpable.

Geoffrey Dixon

417. **Pre-operative Cortisone for Vaginal Fistulas.** By C. G. COLLINS and F. B. JONES. *Obstet. Gynec.*, **9**, 533–537. May 1957. 5 tables. 8 refs.

The authors used cortisone treatment with antibiotics in cases of pelvic infection of the type labelled "ligneous cellulitis" with success. Their success stimulated them to use similar pre-operative treatment in cases of fistula. A total of 3 g. of cortisone was administered in 10 days together with penicillin and a broad-spectrum antibiotic. The cases included 9 vesico-vaginal, 1 recto-vaginal, and 1 rectocervico-vaginal fistula. Treatment allowed surgical repair of the fistulae to be successfully carried out within 4 weeks.

Cortisone is an anti-inflammatory hormone and its use in this type of case allows the surgeon to operate very much sooner than he normally would.

J. G. Dumoulin

418. **Treatment for the Surgically Ligated Ureter.** By J. H. KAMHOLZ, D. D. REISMAN and H. I. KANTOR. *Obstet. Gynec.*, **9**, 599–604. May 1957. 1 fig. 43 refs.

It is a common belief that if a ligature is inadvertently placed round a ureter at operation the simple removal of the ligature is of little value if the injury is more than 12 hours old. The authors refute this belief and illustrate their point by quoting 5 cases. The time between the two operations in these cases was 4, 4, 6, 7 and 33 days.

The method used was carried out in conjunction with a urologist. A ureteric catheter was passed through a cystoscope up to the point of obstruction. The abdomen was re-opened and the tip of the catheter identified. The sutures were removed and the catheter passed on up the ureter. It was left in place for 8 to 31 days, acting as a splint. Sometimes it is advisable to insert an extra peritoneal drain.

The result in all cases was uniformly good.

J. G. Dumoulin

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